Universitat de Girona
Facultat de Medicina

EVALUATION OF THE COMBINATION OF MAGNETIC RESSONANCE IMAGING AND ARTIFICIAL INTELLIGENCE IN THE DIAGNOSIS OF ENDOMETRIOSIS

A cross-sectional study

FINAL DEGREE PROJECT

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1. ABBREVIATIONS

AI	Artificial Intelligence
CA 125	Cancer antigen 125
CEIC	Clinical Research Ethics Committee
COX-2	Cyclooxygenase 2
DIE	Deep infiltrating endometriosis
E2	Estradiol
GNRH-AS	Gonadotropin-releasing hormone
ILs	Interleukins
MRI	Magnetic Resonance Imaging
NSAIDs	Nonsteroidal anti-inflammatory drugs
OMA	Ovarian endometriomas
PACS	Picture Archiving and Communication System
PGEs	Prostaglandins
POD	Pouch of Douglas
rASRM	revised American Fertility Society for Reproductive Medicine
RVS	Rectovaginal septum
SUP	Superficial peritoneal lesions
TNF	Tumour necrosis factor
TVUS	Transvaginal ultrasound
USL	Uterosacral ligament

2. ABSTRACT

BACKGROUND

Endometriosis is an inflammatory oestrogen-dependent condition characterized by the presence of endometrial tissue outside the uterus. It affects women during childbearing age and has an association with pelvic pain and infertility. Despite a range of symptoms, diagnosis of endometriosis is often delayed due to a lack of non-invasive, definitive tools for the diagnosis of endometriosis.

Traditionally, endometriosis was diagnosed by an exploratory laparoscopy with posterior histology analysis. Nowadays new diagnostic strategies are arising such as Transvaginal ultrasound (TVUS) due to its availability and low cost. Although ultrasound can diagnose most locations, its limited sensitivity for posterior lesions does not allow management decisions in all patients. MRI has shown high accuracies for anterior and posterior pelvic endometriosis and enables complete lesion mapping before surgery. Moreover, adding an artificial intelligence (AI) analysis system to the MRI description can provide the expert review that lacks in tertiary centres or other centres where there are no specialised radiologists in endometriosis.

OBJECTIVE:

To evaluate the accuracy of artificial intelligence analysis combined with MRI in comparison with the Gold Standard technique, exploratory laparoscopy, in the diagnosis and staging of endometriosis.

METHODS:

This protocol study is designed as a cross-sectional retrospective study. Pre-surgical MRIs of 30 female patients who have been diagnosed with endometriosis by laparoscopy in Girona during 2005 -2021 will be re-analysed by an AI analysis system in order to compare the AI + MRI with the Gold Standard, diagnostic laparoscopy.

KEYWORDS:

Endometriosis, MRI, Artificial Intelligence Analysis System, Deep Infiltrating Endometriosis, Superficial Peritoneal endometriosis, Ovarian endometriosis, Diagnostic laparoscopy.

3. INTRODUCTION

3.1. ENDOMETRIOSIS

3.1.1 DEFINITION

Endometriosis is an inflammatory oestrogen-dependent condition characterized by the presence of endometrial tissue **outside the uterus**. It affects women during childbearing age and has an association with pelvic pain and infertility (1).

Incidence of endometriosis stands between 6% to 10% in fertile women, 30 to 80% in women with infertility and 30 to 80% in women that suffer from chronic pelvic pain (2). However, these data are not straightforward as it has been stated that there is a delay of 7 to 10 years of identification of the disease once the patient begins with symptoms, due to the variety of symptoms and difficultness of diagnosis (3,4).

3.1.2. ANATOMICAL LOCATIONS

The most common locations are on the pelvic peritoneum, ovaries and rectovaginal septum which are described in literature such as **superficial peritoneal lesions** (SUP), **ovarian endometriomas** (OMA) and **deep infiltrating endometriosis** (DIE) (*Figure 1*). Nonetheless, there are other areas where endometrial tissue is found such as the pleura, pericardium and brain, but these locations are extremely infrequent (3,5).

SUP, DIE and OMA are differentiated by their location but also by their histological and clinical characteristics. SUP is the least severe form of endometriosis, the lesions extend to the serosa layer of the structures in the pelvic cavity. Whereas, in DIE lesions extend more than 5mm into the peritoneal surface (affecting structures such as uterosacral ligaments) or arrive to the muscular layer of the organs surrounding the uterus like the bladder, intestine or ureter (3,6).

Invasion of the myometrium with endometrial tissue is called adenomyosis that differs from endometriosis. Adenomyosis can coexist with endometriosis and although they are both defined by the implantation of ectopic localization of endometrial cells their association is not well established (3).

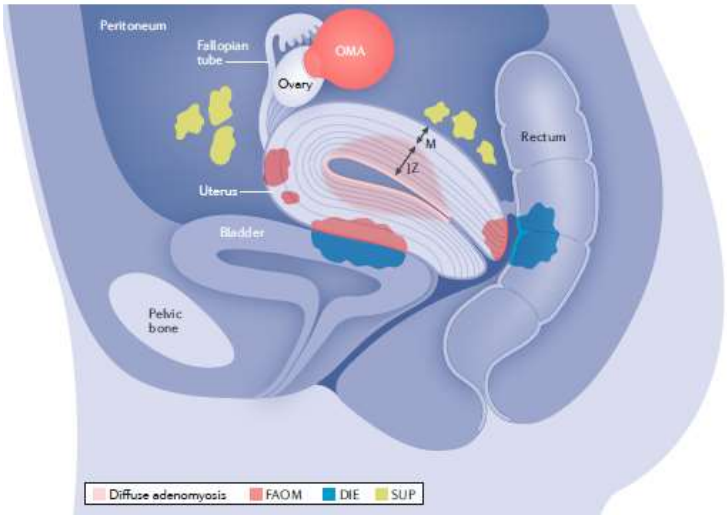

Figure 1: Different types of endometriosis and adenomyosis. SUP: superficial peritoneal endometriosis, OMA: ovarian endometriomas, Deep infiltrating endometriosis (DIE), focal adenomyosis of the outer myometrium (FAOM), Junctional Zone (JZ), myometrium(M). Extracted from (3).

3.2. ETHIOPATHOGENESIS

Through evolution, multicellular life forms have set essential standards of differentiation represented by assumptions for cells to follow on the way toward tissue development:

- Fix their DNA when harmed by either intrinsic or extrinsic factors
- Divide when receiving signals from neighbours
- Live in their appointed location

Endometriosis doesn't submit to the third essential evolutionary rule. Regardless of whether driven by intrinsic or extrinsic powers, endometriosis cells appear to have lost association with their native location (6).

Theories that try to explain the pathogenesis of endometriosis take into account how endometrial cells are dispersed through the abdominal cavity. Endometriosis is a multi-etiological disease (*Figure 2*), nowadays four main theories try to explain the pathogenesis of endometriosis.

1. **Retrograde menstruation**

Sampson stated in 1920s that endometrial implants observed onto the peritoneum are caused by viable fragments that are driven through the Fallopian tubes while uterine

contractions occur and once they arrive at the peritoneal cavity they can be deposited onto pelvic structures(1,5). This hypothesis is clarified by 3 factors: the presence of retrograde menstruation, the feasibility of endometrial cells in the peritoneum and the capacity of endometrial cells to adhere, multiply and proliferate (7).

A case-control study done by Silvia Vannuccini et al. determined that premature birth, formula feeding, preeclampsia, smoking during pregnancy, endometriosis or uterine fibroids present in the mother of patients with endometriosis might cause ontogenic disruption while endometriosis programming is taking place. The result of this disruption are the pathological endometrial fragments that contribute to retrograde menstruation (8).

An increase in blood flow, early age of menarche as well as short cycles are hazard factors for endometriosis that contribute to retrograde menstruation (3).

Retrograde menstruation evidence relies on anatomical distribution and the effect of gravity. The evidence showing that lesions of DIE endometriosis are located in the pelvis rather than the abdomen demonstrated in a study of 426 patients that had major distribution in uterosacral ligaments and the Pouch of Douglas shown by MRI. Resulting also in fewer lesions on the bladder as it is situated in the anterior compartment above the Pouch of Douglass (POD) (9).

Other theories should be taken into consideration in addition to retrograde menstruation, as this phenomenon has been proved to be common among women who did not suffer from endometriosis (10).

2. Endometrial stem cell implantation

Through retrograde menstruation, endometrial epithelial progenitors and mesenchymal stem cell-like cells are implanted in the peritoneum (1)**.**

3. Müllerian remnant abnormalities

When looking at the uterus' embryology it comes from the Müller Conducts. This theory states that during the embryology transformation remains are left in the peritoneal

cavity therefore once puberty starts and oestrogens levels start to increase these embryologic remains develop themselves into endometriotic lesions (11).

Muller's theory could be the one explaining the atypical location of endometriosis or its presentations in women at prepuberal ages or even in men (12).

4. **Coelomic metaplasia:**

Endocrine-disrupting chemicals stimulate the differentiation of peritoneal cells into endometrial cells producing the change of peritoneal tissue to ectopic endometrial tissue (11).

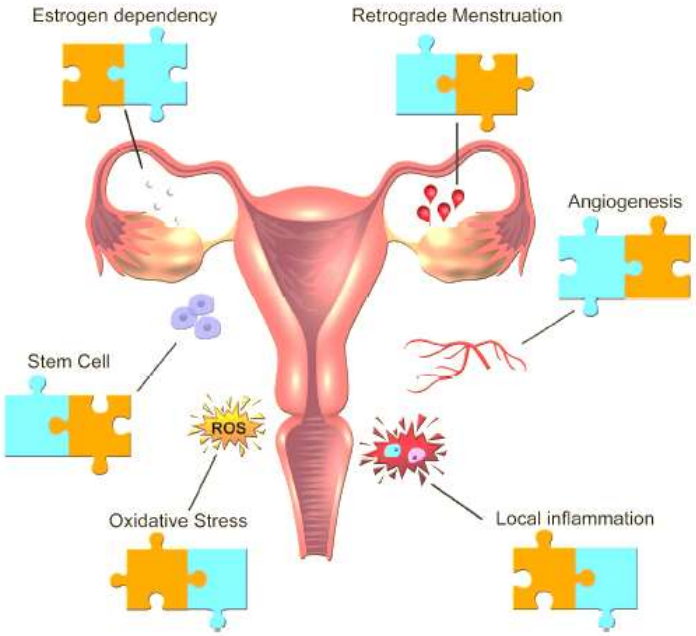

Figure 2: Endometriosis characteristics. Legend: Endometriosis main characteristics and contributions to its knowledge – shown as puzzle pieces – coming from studies using animal (blue pieces) or human – based models (orange pieces). Extracted from (15).

Once taken into account all these theories, what becomes clear is that endometriosis has to be produced by a combination of them. It seems that it is a 'two-stage' theory where retrograde menstruation seems to be necessary but also inflammatory, hormonal and immunological factors have to be implied for the implantation of endometrium to take place (13).

3.2.1 INFLAMMATION IN ENDOMETRIOSIS

It has been proven that endometriosis is also an inflammatory disease that leads to fibrotic lesions which are responsible for most of the clinical symptoms. Eutopic endometrial tissue responds to changes in oestrogen which leads to its shedding during every menstrual cycle, the main difference with ectopic endometrial tissue is that this one remains in its abnormal location during every cycle leading to accumulation of blood inside endometriotic lesions.

Accumulation of blood leads to the production of reactive oxygen species that initiate cell death, inflammation and prime the peritoneal surface for adherence by retrograde endometrium or progenitor stem cells. When comparing eutopic endometrium to ectopic endometrium COX-2, IL-1β, IL-8, tumour necrosis factor (TNF)- α, PGE2 and E2 are increased in the second type supporting the fact that endometriosis causes inflammation. The next step is the recruitment of inflammatory cells such as hemosiderin macrophages and secretes mediators that maintain inflammation. All this process can lead to the conversion of inflammatory tissue to fibrotic tissue which is observed as adhesions through laparoscopy (6).

3.3. DIAGNOSIS

3.3.1 CLINICAL DIAGNOSIS

Endometriosis presents itself with a wide variety of symptoms (*Table 1*) that do not always correlate with the gravity of the lesions, or even with asymptomatic endometriosis therefore diagnosis with only clinical history can be challenging and non-reliable due to its heterogenicity, and overlapping with other conditions such as irritable bowel syndrome and pelvic inflammatory disease (12,14). Most prevalent symptoms in endometriosis are pain and infertility (15).

The most common symptoms presented in endometriosis are:

- **Pelvic pain**: Cyclic pelvic pain can be presented as dysmenorrhea (75%), deep dyspareunia (44%) and pelvic pain unrelated to intercourse or menstruation, such as dyschezia and dysuria(3,12,16). It is the main symptom in endometriosis

but also the cardinal symptom in many other gynaecological problems therefore can be misled by professionals into other pathologies (3,12). Nevertheless, a chronic, cyclic, persistent, with worsening of the symptoms through time has to make the physician think of endometriosis (17).

- **Intestinal or urinal symptoms:** Alterations in depositional rhythm, blood in faeces, abdominal distension, haematuria, tenesmus, discomfort sensation could be the symptoms of a rectal or vesical affectation.

- **Menarche alteration:** hyper menarche is the most common alteration in patients with endometriosis but these alterations can also be presented as changes in the frequency in between periods, irregular cycles and premenstrual spotting (17).

- **Infertility:** This can be caused by anatomical changes, formation of adhesions and the presence of ovarian cysts. The overproduction of inflammatory mediators can negatively influence the function of the oocyte and decrease the endometrial receptivity (2).

- **Others:** low back pain, sciatica, cyclic pain in the shoulder, pain in the right iliac fossa, bleeding, pneumothorax or pain in previous surgical areas that could make the physician think of extra pelvic sites for endometriosis.

The combination of these symptoms should make physicians consider the presence of endometriosis despite the low specificity of these, and should deriver patients to specialised centres (12).

Table 1. Specific locations of deep endometriosis, their frequency and corresponding associated symptoms. Extracted from 241 patients with 344 pathologically proven lesions of deep endometriosis. Adapted from (18).

ANATOMICAL LOCATION	FREQUENCY	CLINICAL SYMPTOMS
TORUS UTERINUS AND UTEROSACRAL LIGAMENT	69,2%	Deep dyspareunia
VAGINA	14,5%	Painful defecation Gastrointestinal symptoms
BOWEL	9,9%	Noncyclic pain Gastrointestinal symptoms
BLADDER	6,4%	Lower urinary symptoms
RECTOVAGINAL POUCH ADHESION	-	Severe dysmenorrhea

Clinical examination

- **Inspection:** search of endometriotic lesions in surgical scars.

- **Exploration:** professionals should be looking for red or bluish lesions on the vaginal fornix or irregularities in the vaginal mucosa.

- **Vaginal examination:** Palpation of sensitive nodules or thickened area involving any of several pelvic locations (torus uterine, uterosacral ligaments, upper third of the posterior vaginal wall and POD). Palpation of adnexal masses, fixed retroverted uterus and, or pelvic pain upon mobilization are physical characteristics of endometriosis (3).

- **Rectal examination:** To determine the presence of nodules, fibrosis or painful locations at the rectum, uterosacral ligaments, parametric and rectovaginal septum (17).

Nonetheless, a normal physical examination does not rule out endometriosis. It is recommended to undergo the clinical examination during the menstruation period as improvement of the detection of the signs has been noticed (3,12).

Differential diagnosis should be done with other pathologies such as chronic pelvic inflammatory disease, uterine leiomyomas, ovarian malignant tumours, gastrointestinal disorders and chronic pelvic congestion syndrome (19). These causes of pelvic pain should be ruled out by performing other diagnostic tests (10):

- Urinalysis
- Pap smear
- Pregnancy test
- Vaginal and endocervical swabs

3.3.2 BIOMARKERS IN ENDOMETRIOSIS

CA 125: Cancer antigen 125 (CA 125) levels are increased in endometriosis. High levels of CA 125 can also indicate other gynaecological diseases such as ovarian cancers (20). Therefore, it has limited clinical utility (2).

3.3.3. DIAGNOSIS USING IMAGE TECHNIQUES

The three main image techniques used in the diagnosis of endometriosis are TVUS, MRI and laparoscopy (*Table 2*).

TVUS is the first technique used, as it has minimum risk and low cost, in the evaluation of women with pelvic pain and infertility(20). TVUS technique is used for the diagnosis of endometriomas and bladder implants but has a limited value in evaluation on peritoneal endometriosis and deep infiltrative endometriosis (16,21) it has a sensitivity of 71-98% and specificity of 92-100% when evaluating pelvic organs (20).

The *International Deep Endometriosis Analysis group* stated the main steps that physicians should take when examination of a patient is being done:

1. Assessment of uterus and adnexa while evaluating the presence or absence of endometriomas.

2. Search for sonographic markers such as specific tenderness and ovarian mobility.
3. Evaluation of the sliding sign in the POD.
4. Search for DIE nodules at anterior and posterior compartments of the pelvis and evaluation of these if found (22).

TVUS can locate endometriotic lesions that are found up to 5mm into the uterine lining showing a hypoechoic mass on the image. Lesions > 5mm in the peritoneum are classified as DIE. 'Tenderness – guided and sliding sign' are the two most used techniques. The first one allows the probe to identify a hypoechoic mass and it describes its depth, the second one predicts the presence of endometriosis in the Pouch of Douglas. Superficial endometriosis and lesions upon the sigmoid region of the colon cannot be detected by TVUS (20).

MRI is considered, after TVUS, as a second-line imaging technique as it has higher costs and reduced availability. It has many advantages as it is less operator-dependent and can evaluate larger structures of the pelvis such as bowel, ureteral or extra pelvic endometriotic lesions (23). It generates multiplanar images and has a high sensibility for detecting fibrine degradation products which can be useful when needing to identify hidden lesions. The sequences used with MRI are:

- T2 weighted sequences in axial, sagittal and coronal planes and one sequence with fat saturation.
- T1 weighted sequence in axial and T1 weighted axial and sagittal with fat saturation.
- Signs of endometriosis: High signal intensity at T1, low at T2 and non-enhancing after gadolinium.
- If there is suspicion of deep endometriosis rectum and vaginal distension is recommended, previous to the exam, by administrating 100-150ml of ultrasonic gel through vaginal route (16,24).

As in TVUS a structured routine read has more sensitivity than a non-structured read, therefore, the pelvis should be divided into the anterior, middle and posterior compartments for a better diagnosis (23).

Laparoscopy is the gold standard method for the diagnosis of endometriosis. The direct observation plus the biopsy confirms endometriosis. Red injuries represent vascularized lesions and are representative of an early stage of the disease. Laparoscopy is used also for staging endometriosis with the revised American Fertility Society for Reproductive Medicine (rASRM) (21). It gives information about the presence of the disease and its extension while giving the opportunity of treating the patient (22). Nonetheless, nowadays laparoscopy is reserved only for when treatment is needed.

Table 2. Diagnostic performance TVUS, MRI and Laparoscopy. Adapted from (23,25).

IMAGING	SENSITIVITY (%)	SPECIFICITY (%)
TVUS	79 (95% CI 69-89)	94 (95% CI 88-100)
MRI	94 (95% CI 90-97)	77 (95% CI 44-100)
Laparoscopy	97,68%	79,23%

ENDOMETRIOMAS

Endometriomas are diagnosed by **TVUS** as diffuse low-level internal echoes with hyperechoic foci in the wall of a multilocular cyst (18). If only low-level internal echoes are present and there is absence of hyperechoic foci in the wall, patients might need other imaging tools to discard malignancy (26).

MRI studies in endometriomas are done in order to exclude a malignant diagnosis. The sequences used are described as high signal intensity at both T1 and T2 weighted sequences persisting at subsequent fat-suppressed T1 weighted images. Fat suppression technique is used to rule out cystic teratomas (*Figure 3*). 'Shading' has been described when there is a low signal intensity on T2 that corresponds to chronic bleeding and can differentiate an endometrioma from a haemorrhagic cyst. When both characteristics are present sensitivity and specificity of diagnosis for endometriomas have been demonstrated to be 90% d 98% respectively (16,18).

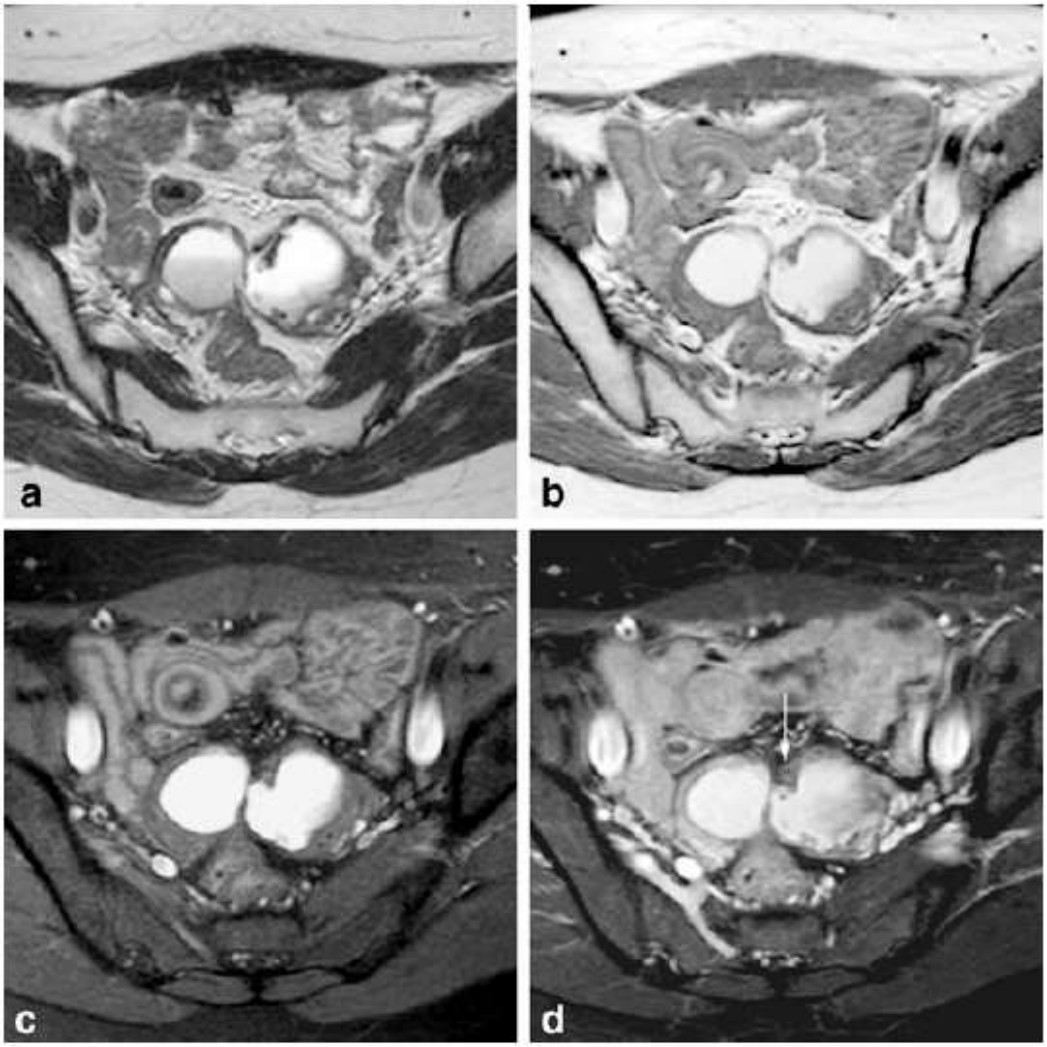

Figure 3. MRI of the pelvis in a 29-year-old woman with dysmenorrhea. **A.** Axial T2-weighted image demonstrates bilateral ovarian cysts with an upper hyperintense content and indistinct internal lesions margin suggestive of intraovarian adhesions ("kissing ovaries"). **B-D.** The same image level as in **A** at different T1-weighted sequences: native T1-weighted (**B**), fat supressed T1-weighted (**C**), and after intravenous contrast enhancement and fat suppression (**D**). The Ty hyperintense content of both cysts persists after fat suppression while the irregular wall of the cyst does not demonstrate enhancement after intravenous contrast injection (*arrow*). Pathology confirmed the diagnosis of endometriosis. Extracted from (18).

Laparoscopy has a sensitivity and specificity of 97% and 95% respectively. Two types of cysts are described when observed by laparoscopy; white or yellowish and dark cyst, this distinction gives information about the maturity of the lesion. Differentiating this type of cysts is also important as different surgical treatments are required (26).

SUPERFICIAL ENDOMETRIOSIS

TVUS has failed to detect superficial endometriosis (26).

MRI has been proven to diagnose SUP only when endometriotic lesions are > 5mm or when there is presence of haemorrhagic cysts that are seen as a hyperintense signal in T1 and hypointense signal in T2 (16). The Bowel or rectum are described as isointense and can lead to mistaken diagnosis when endometriotic lesions are also isointense.

Laparoscopy is recommended with hydro floatation rather than gas insufflation as it can cause the collapse of adhesions and vessels. Lesions diagnosed by laparoscopy are described as flame-like lesions, popular or vesicular lesions, fibrotic lesions, peritoneal defects, among others. Considering all the possible descriptions, further biopsy is recommended to rule out benign or malignant lesions that are not endometriosis (26).

DEEP INFILTRATING ENDOMETRIOSIS

For a correct pelvic examination for endometriosis, the pelvis has to be divided into the anterior (bladder and ureters) and posterior compartment (cervix, uterosacral ligaments, rectovaginal septum, fornix, vaginal wall and rectosigmoid).

TVUS objective is to identify and describe as many endometriotic lesions as possible. Endometriotic nodules are described as hipoecoic and solid, they are rarely described as cystic and with irregular or spiculated borders. For better visualization of the bladder, a minimum amount of urine is required in order no lower the false negatives as it enables a better vaginal walls visualization. The rectosigmoid has to be evaluated individually from the anal sphincter to the distal sigma. Endometriotic lesions in the rectosigmoid are described as an enlargement of the rectal muscular layer with or without the involvement of the submucosa (27).

MRI signs for the diagnosis of deep endometriosis are:

- Torus uterine: Visualization of a mass in the upper mid-portion of the posterior cervix.
- Uterosacral ligament (USL): When comparing one ligament to the other, the one affected with endometriosis is visualized by a fibrotic thickening or nodule. If both ligaments are affected, they are described as arciform (*Figure 4*).
- Vagina: abolition of the hypointense signal of the posterior wall or posterior fornix on T2 images, with a mass behind the wall.

- Rectovaginal septum (RVS): Visualization under the peritoneum of a nodule or mass.
- Rectosigmoid: Loss of the hypointense signals on the anterior wall of the rectum/sigmoid colon on T2W images. Replacement of fat tissue between uterus and rectum by a mass that forms an obtuse angle with the wall of the rectosigmoid (*Figure 5.a and 5.b*).
- Pouch of Douglas: Partial or complete disappearance with presence or absence of suspended fluid collection.
- Parametrium: Low-signal intensity area on T2W MRI in the paracervical region.
- Bladder: Nodule or mass usually located at level of the vesicouterine pouch, forming an obtuse angle with the bladder wall. Extension of endometriosis through the bladder wall is described as the loss of hypointense signal of the wall on T2W (*Figure 6.a and 6.b*).
- Round ligament: Endometriosis is diagnosed when the ligaments fibrosis measures > 1cm when compared to the contralateral ligament (28).

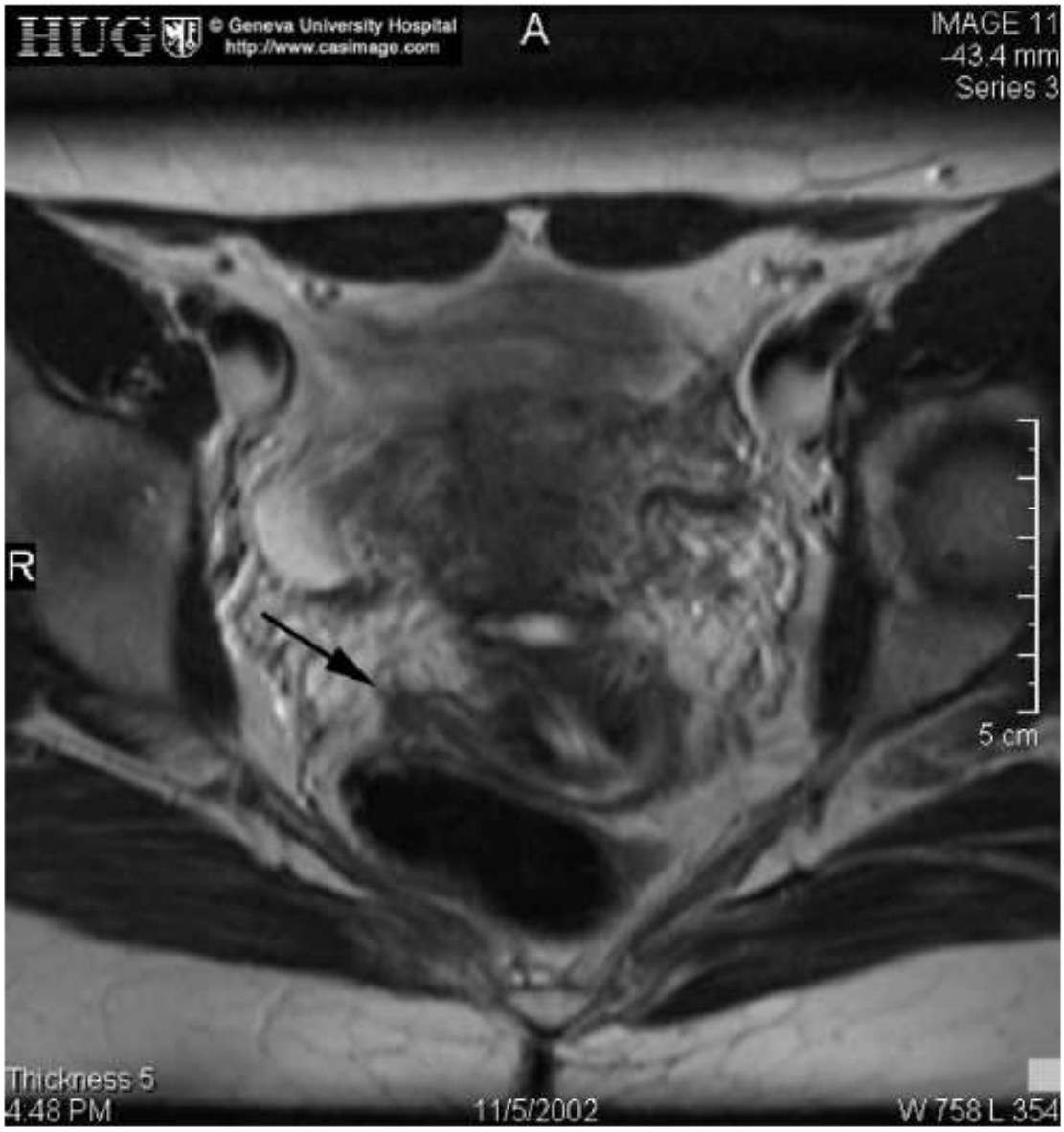

Figure 4. Axial T2-weighted spin-echo MRI of a 32-year-old patient complaining about dyspareunia. The right uterosacral ligament demonstrates nodular thickening with spiculated borders (*Black arrow*). Histology after surgical resection diagnosed endometriosis of the right uterosacral ligament. Extracted from (26)**.**

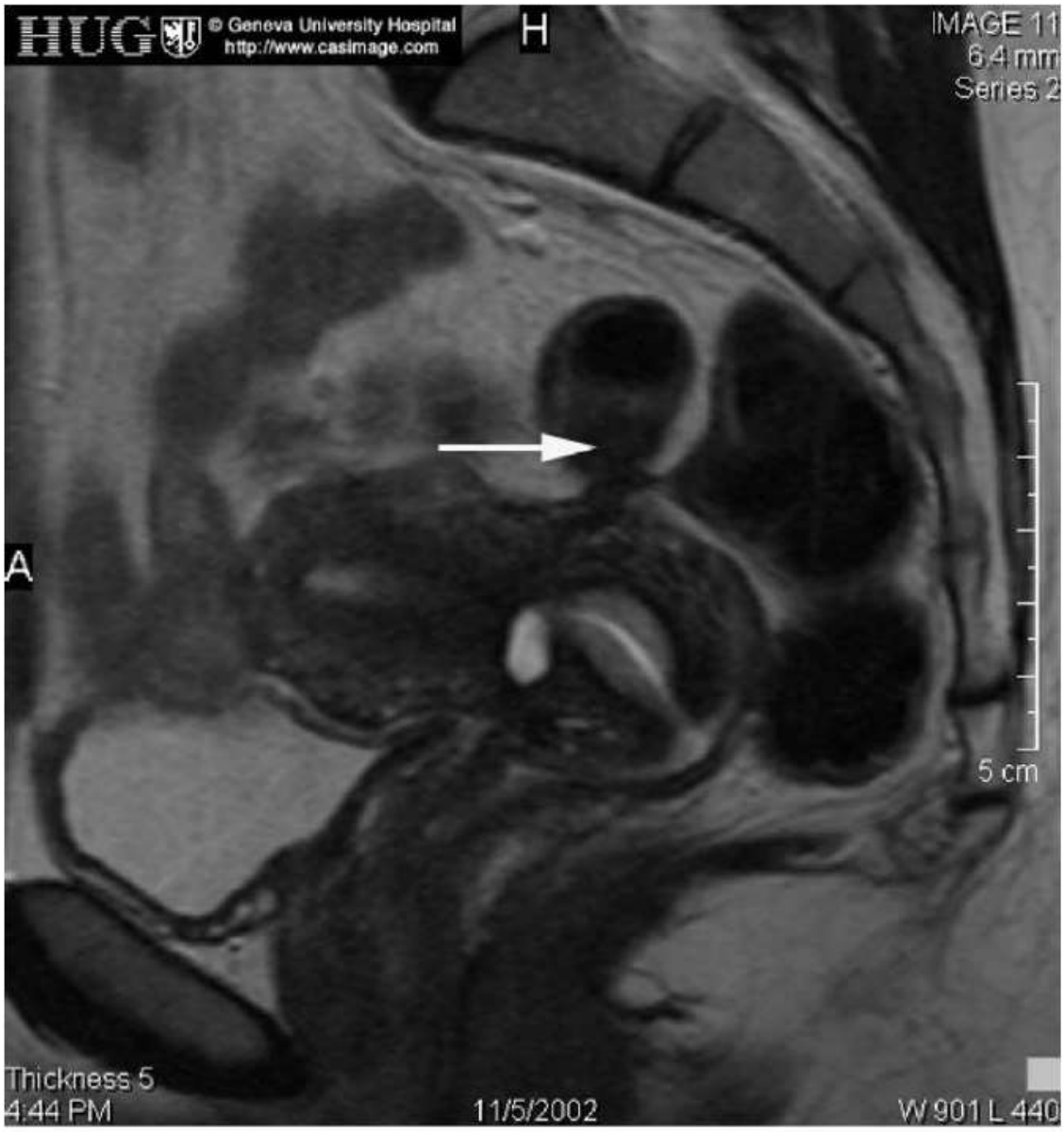

Figure 5.a T2-weighted spin-echo MRI in (**5.a**) the sagittal and (**5.b**) the coronal imaging planes of a 36-year-old woman with painful defecation. (**5.a**) Show hypointense nodule at the posterior part of the uterus, in the pouch of Douglas, extending into the anterior wall of the sigmoid colon (*white arrow*). (**5.b**) Confirms asymmetric thickening of the lower portion of the sigmoid colon wall (*white arrow*) in the coronal imaging plan above the cervix. Extracted from (26).

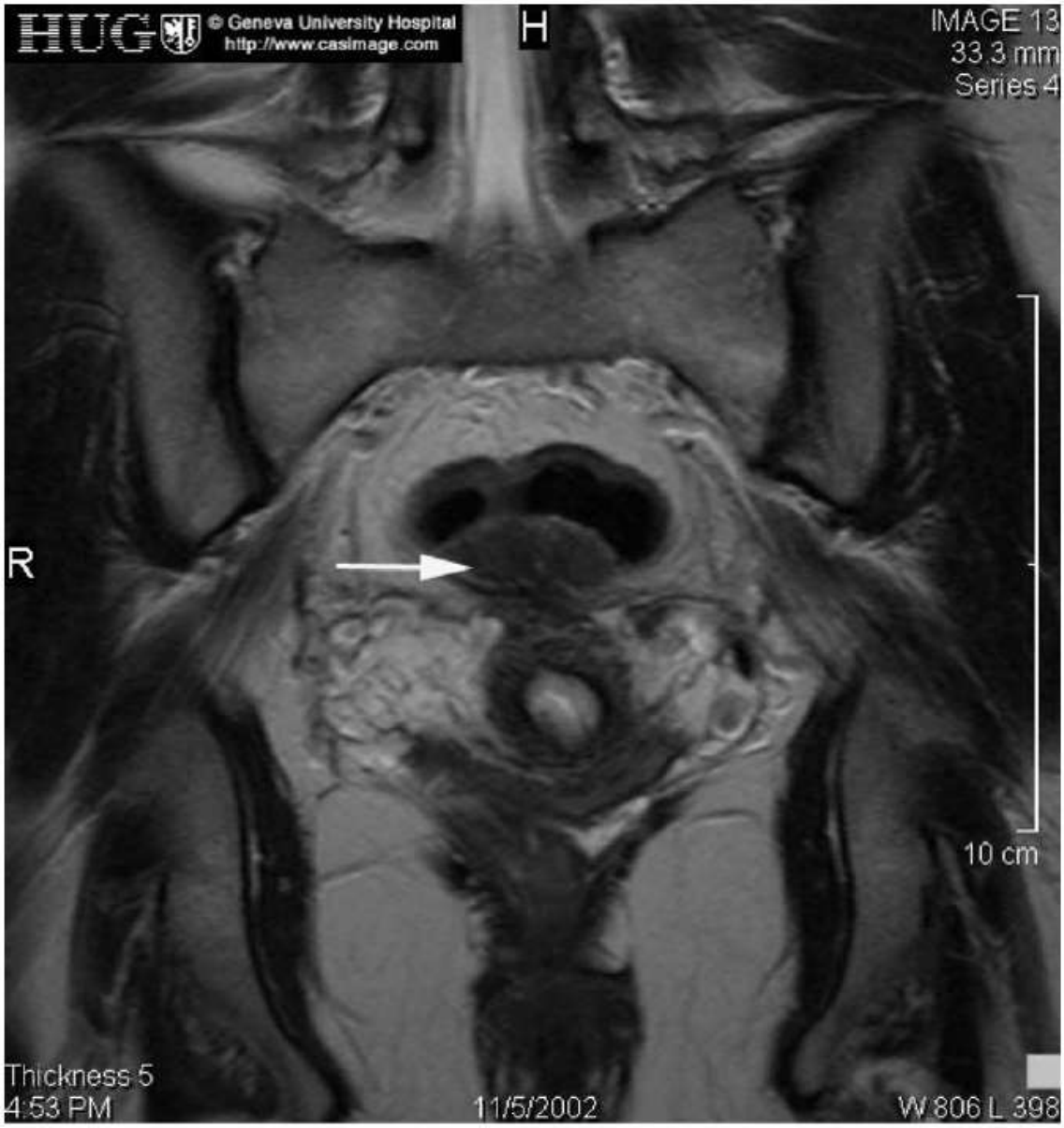

Figure 5.b. (continued). Extracted from (26).

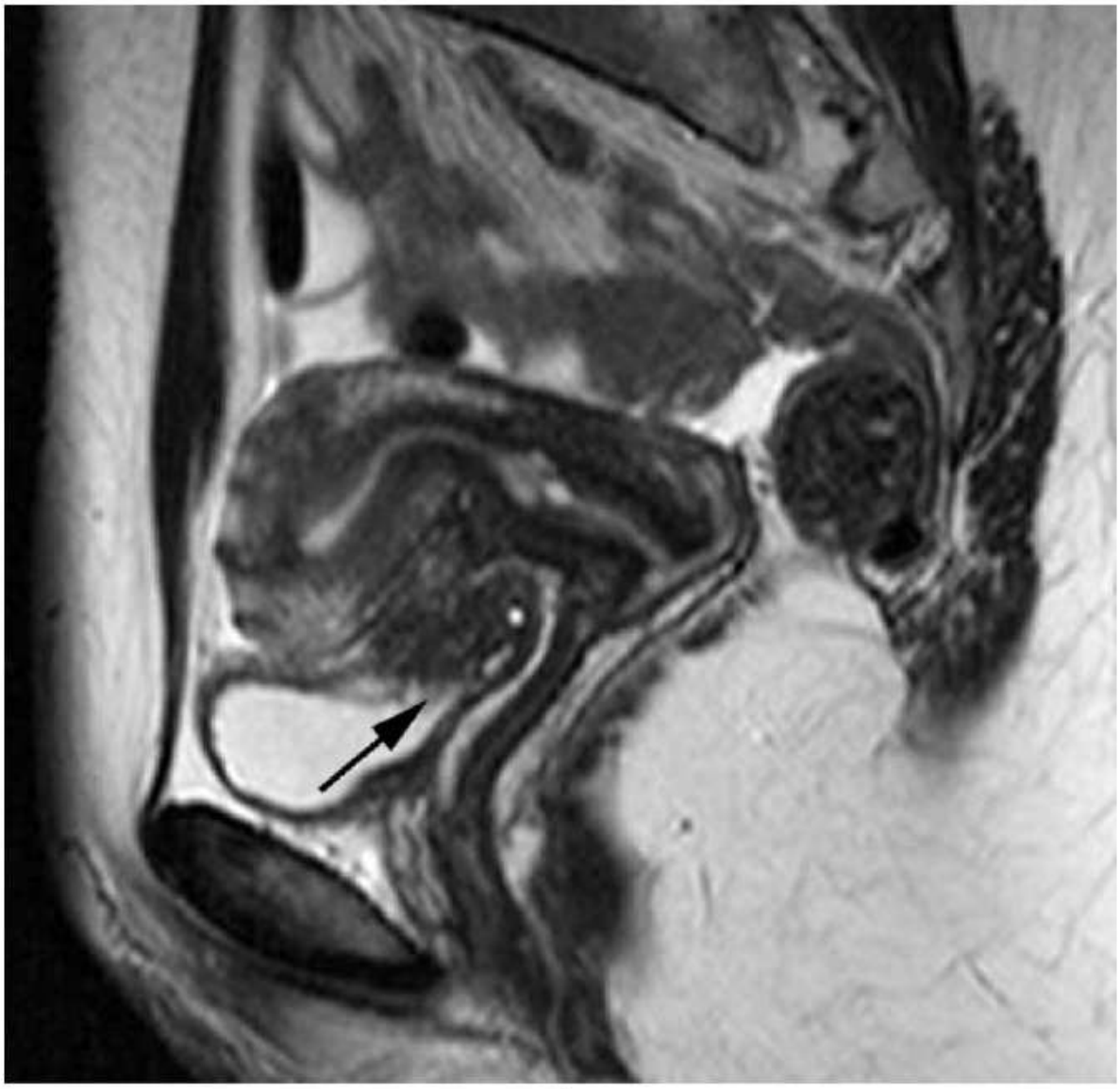

Figure 6.a. Bladder endometriosis confirmed by subsequent partial cystectomy and demonstrated preoperatively at T2-weighted magnetic resonance images in a 29-year-old patient with painful micturition during menstruation. (**6.a**) The sagittal imaging plain shows a hypointense and heterogeneous thickening of the posterior bladder wall (*black arrow*). (**6.b**) The coronal imaging plane shows a hyperintense spot at the lower top of the bladder endometriosis (*black arrow*). Also note the heterogenous structure of the lower portion of the myometrium, which suggests associated adenomyosis. Extracted from (26).

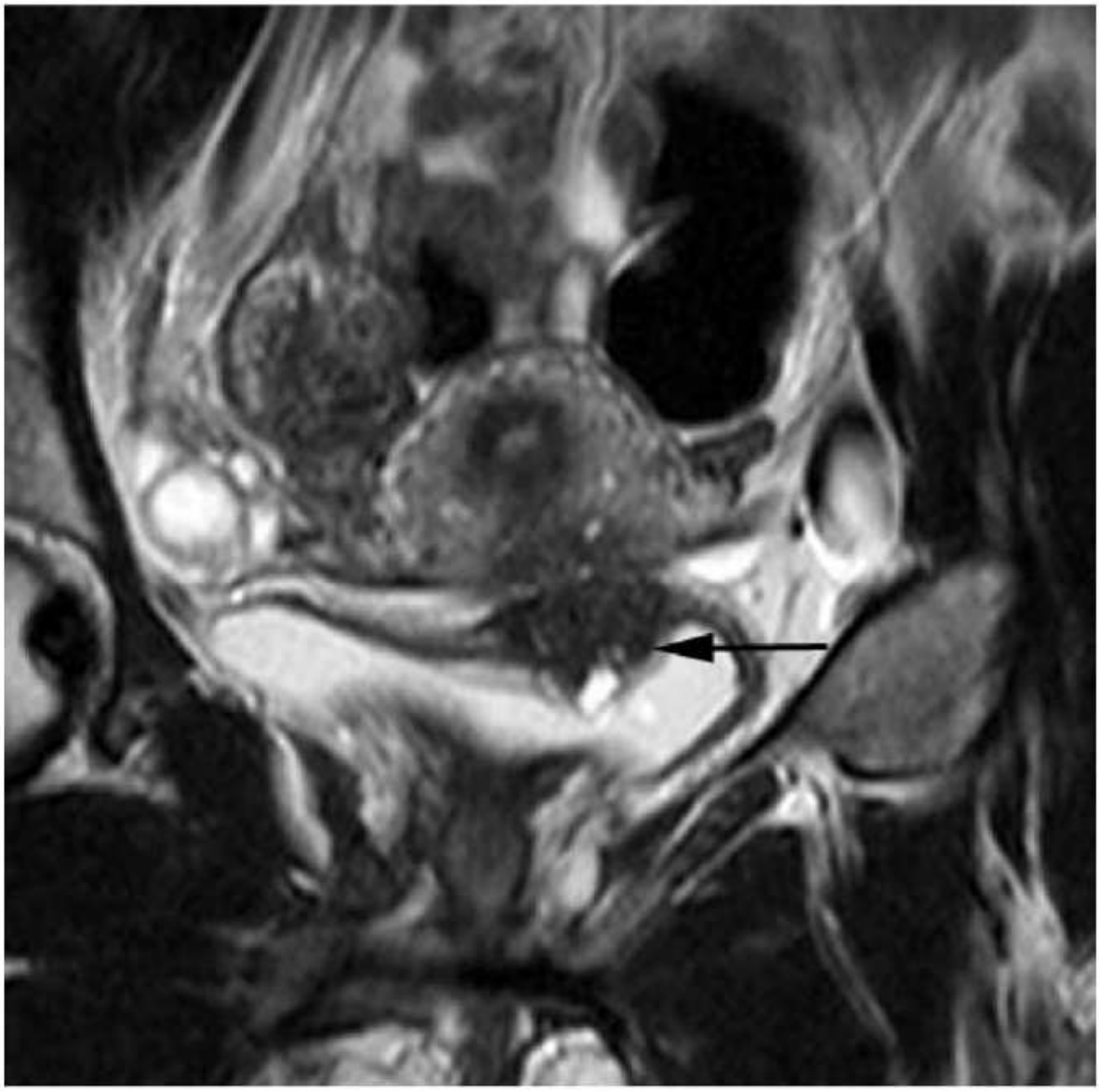

Figure 6.b. (continued). Extracted from (26)**.**

Laparoscopy can describe retraction of the peritoneum or a depthless pouch of Douglass as signs of endometriosis in the posterior pelvis compartment. What laparoscopy cannot describe are the depth and extent of endometriotic lesions in the posterior compartment of the pelvis unless surgery is performed (26).

3.4 HISTOPATHOLOGY

3.4.1 MACROSCOPIC CHARACTERISTICS:

Endometrial peritoneal lesions are diagnosticated by direct perception as dull or blue sore as the aftereffect of blood colouring. Atypical lesions are also described as flame injuries, petechiae and areas of hypervascularization affecting mostly to the uterosacral ligament.

Two types of ovarian injuries have been described such as adherences, which are superficial, or endometriomas (21).

3.4.2 MICROSCOPIC CHARACTERISTICS:

Endometriosis histology is ordinarily characterized by extrauterine lesions consisting of endometrial glands, endometrial stroma. Both should be observed in order to realize the endometriosis diagnostic although stroma is only identified sometimes as the endometrial glands tend to disappear. Endometrial glands grow unpredictably in response to hormonal boost, unlike eutopian endometrium. Hemosiderin-loaded macrophages can be detected due to their inflammatory component (21,29).

3.5 CLASSIFICATION

Endometriosis' classification is done through observation during surgery by the revised **rASRM** classification which was accepted in 1996 and substituted the American Fertility Society classification proposed in 1979 (*Annex 1*).

Lesions in the ovaries and peritoneum are evaluated and given punctuation depending on their size. Adhesions in the ovaries and Fallopian tubes are also assigned to a punctuation. Once all the points are added up it results in 4 stages of classification:

- Stage I (minimal): 1-5 points
- Stage II (mild): 6 -15 points
- Stage III (moderate): 16-40 points
- Stage IV (severe): >40 points

The SARM classification only evaluates superficial and ovarian endometriosis without evaluating DIE or any clinical symptoms. Therefore, the severity of the classification does not provide any information regarding pain and sterility (22).

In 2005 **the Enzian classification** (*Annex 2*) was made in order to complement the rASRM score, by describing DIE which lacks in the rARSM classification. In 2011 the revised Enzian classification was published as the first one was too complex (30).

The Enzian score divides retroperitoneal structures into:

- A: rectovaginal septum, vagina
- B: sacrouterine ligament to the pelvic wall
- C: rectum, sigmoid colon

Lesions are also measured and classified in different grades depending on their size:

- Grade 1: <1cm
- Grade 2: invasion 1-3cm
- Grade 3: invasion >3cm

DIE under the pelvis is classified by the prefixes 'F' that means far, referring to the retroperitoneal distant locations, and then another prefix is added referring to the organ involved (FA= adenomyosis, FB= involvement of the bladder, FU= intrinsic involvement of the ureter, FI= bowel disease cranial to the rectosigmoid junction and FO= other locations) (31).

3.6 TREATMENT

The four main objectives of the treatment for endometriosis are:

1. Suppression of pain
2. Regain fertility
3. Eradicate visible endometriosis
4. Stop the progression of the disease

3.6.1. MEDICAL MANAGEMENT

Nowadays no monotherapy can achieve these four principles, that is why the combination of different therapies is taken into account. These combinations are thought regarding each drug's benefits and side effects (*Table 3*). Endometriosis should be considered a chronic disease until menopause therefore the treatment given to the patients has to be effective and secure. It also has to be adequate for each woman and has to be individualized for each one of them (12).

- **NSAIDs**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first option of treatment for reducing pelvic pain and dysmenorrhea. NSAIDs action mechanism works by inhibiting the enzyme COX, which produces PGs, ILs and cytokines which are responsible for pain(2). Nonetheless, monotherapy with NSAIDs has minimal effectiveness in patients with endometriosis (32).

- **Hormonal treatment**

Hormonal treatment reduces pain significantly after 6 months of treatment, nonetheless recurrence of symptoms is frequent after suspension of treatment. Ovulation suppression, decrease in menstruations frequency or the generation of amenorrhea are the mechanisms that reduce pain associated with endometriosis (33). This leads to a hypoestrogenic state which reduces the conversion of arachidonic acid to prostaglandins resulting in lower pelvic pain and dysmenorrhea (32).

Combined oral contraceptives, **progestins** or **Gn-RH** analogues are considered efficient for reducing pelvic pain caused by endometriosis. However, GnRH analogues are considered second-line treatment because of their secondary effects on bone mass after a 6-month treatment (34).

Danazol is an oral androgenic agent that supresses the hypothalamic-pituitary-ovarian axis causing amenorrhea by lowering oestrogen and increasing androgen levels in serum. The outcome of its mechanism is the interruption of the ovarian cycle and in consequence interfering in the pathogenesis of endometriosis. It has limited use at it has proven low tolerability.

Aromatase inhibitors supress the conversion of androgens to oestrogens as aromatase is a cytochrome P450 enzyme that catalyses the synthesis of oestrogens from androgens. Studies have shown that at 24 months after GnRH treatment with aromatase inhibitors patients related more reduction of pain symptoms rather than with only GnRH monotherapy (33).

Table 3. Current drug class of the treatment of endometriosis extracted from (35).

DRUG CLASS	ADVANTAGES	DISADVANTAGES
NSAIDs	- First line therapy - Efficacious in improving moderate women pain symptoms - Not expensive	- They only act on symptoms - Does not block of ovulation
Estroprogestins	- First-line therapy - Not expensive - Low rates of AEs - Multiple route of administration available	- Between one-fourth and one-third of patients treated do not respond to them
Progestins	- First-line therapy - Not expensive - Lower thrombotic risk - Low rates of AEs - Multiple route of administration available	- Only two progestin approved for contraception purpose (DSG, ENG-subdermal implant and LNG-IUS) - Between one-fourth and one-third of patients treated do not respond to them
Gn-RH-as	- Secondary-line therapy (efficacious in treating patients who did not respond to COCs or progestins)	- Not oral administration (subcutaneous) - Expensive - High rate of AEs (oestrogen-related)
Danazol	- Not expensive	- Low popularity due to the androgenic AEs
Aromatase inhibitors	- Efficacy in women refractories to other traditional hormonal treatments (should be used only in scientific setting)	- Expensive - High rates of AEs (myalgia, osteoporosis etc.)

GnRH-as = gonadotropin-releasing hormone agonists; GnRH-ant= gonadotropin-releasing home antagonists; AE = adverse effects; DSG = desogestrel; ENG= etonorgestrel; levonorgestrel releasing intrauterine device.

3.6.2 SURGICAL MANAGEMENT

- **Superficial endometriosis**

Laparoscopic treatment should be done on all patients who have not responded to medical treatment (36). Laparoscopic vaporization is the indicated technique as it has proven to be the most effective surgical method in pain relief while maintaining non-endometrial tissue. Dysmenorrhea, dyschezia and chronic pelvic pain are shown to be superiorly reduced by excision of the endometriotic lesions rather than with coagulation techniques (37).

- **Ovarian endometriosis**

Surgical management of ovarian endometriosis should be individualized depending on patient's age, pregnancy desires, family background of ovarian cancer and type of endometriomas (36,37).

If pain is the main reason for surgical treatment of endometriomas ovarian cystectomy should be done as it has proven to reduce endometriosis-associated pain as well as lower recurrence rate (36).

Women who desire to regain fertility can take profit from a surgery that consists of scission of endometriomas and restoring its anatomy. Inhibition of ovulation by medical treatment is required before surgery in order to avoid the removal of functional cysts that might appear as endometriomas (37).

- **Deep infiltrating endometriosis**

Surgical indication for DIE depends on symptoms, infertility and other characteristics such as intestinal or ureteral obstruction (32,38). In order to proceed correctly through the surgery, a systematic approach is needed in all patients. It starts with correct identification and dissection of the anatomy such as the two ureters, the hypogastric nerves and the uterosacral ligaments (39). As DIE is highly vascularized and deeply infiltrating, as its name indicates, it is necessary hormonal suppressive treatment before surgery as it will allow the surgeon to proceed with better space for dissection by decreasing inflammation (37).

When surgery involves dissection of the uterus patients with genesis desires that have not been accomplished will undergo the most conservative surgery as possible while patients who have already accomplished their desire will undergo a hysterectomy and if the patient is over 40 years old an adnexectomy can be also realized.

When DIE involves the urinary tract different techniques are required depending on the location of endometriotic lesions. Partial cystectomy is preferred for deep injuries involving the bladder whereas colocation of stents is preferred if the trigon is affected. Endometriosis located at the ureters can be treated by resecting the injuries if located externally. When they involve the interior of the ureter, scission is not enough therefore it has to be followed by an end-to-end anastomosis or ureteral reimplantation.

If endometriotic lesions affect the bowel there are different options for treatment.

- Shaving: consist in resecting the superficial lesions of the wall without arriving to the intestinal lumen.
- Discoidal resection: This technique is only used when only one endometriotic node is located that measures <3,5cm and are located in the anterior wall of the intestinal lumen.
- Segmentary resection: Reserved for when the patient suffers from more than one endometriotic node that measures <2cm or when only one measures >3,5cm. It consists of resecting part of the bowel and doing and end to end anastomosis (38).

4. JUSTIFICATION

Endometriosis is estimated to surpass 50% prevalence in women with infertility and chronic pelvic pain. The mean interval between symptoms onset and clinical diagnosis is estimated at 7-10 years. The increased diagnostic delays further complicate outcomes for these patients by worsening symptom chronicity, therefore contributing to its socioeconomic implications and negative impact on quality of life (4).

Undergoing a diagnostic laparoscopy is not exempt from risks as it is an invasive procedure. Laparoscopy has also its downsides, for instance, the inability to detect endometriosis when its appearance can be mistaken for other lesions and its incapacity of describing the depth of the lesion or the extent of organ involvement (4,23).

Regarding diagnostic laparoscopy's disadvantages new strategies are arising such as "see and treat". Significant advances in imaging techniques have proven that they are able of mapping endometriosis for preoperative planning (36).

Transvaginal ultrasound has proven to be the standard method for this purpose as it has good sensitivity and specificity, availability and low cost. However, MRI staging for endometriosis is evolving, especially in DIE staging. In addition, distinct advantages as a cross-sectional imaging method, including less operator dependency and higher reproducibility are offered by MRI (4,36).

Improvements in non-invasive tools for diagnosis in endometriosis can empower both surgeon and the patient to engage in better preoperative planning and can allow patients to make a properly informed decision (22). A crucial inconvenience for non-expert endometriosis radiologists in endometriosis is the lack of experience when diagnosticating the lesions. Expert guided imaging improves the diagnosis of endometriosis therefore it should be provided to all patients for counselling and surgical plan (4).

Adding the AI analysis system to the MRI description can provide the expert review that lacks in tertiary centres or other centres where there are no specialised radiologists in endometriosis.

5. QUESTION

Can MRI combined with an artificial intelligence analysis system provide similar diagnosis and staging results as the gold standard of surgical laparoscopy?

6. HYPOTHESIS

MRI combined with an artificial intelligence analysis system provides a similar diagnosis and staging results as the gold standard of surgical laparoscopy.

7. OBJECTIVE

To evaluate the accuracy of artificial intelligence analysis combined with MRI in comparison with the Gold Standard technique, exploratory laparoscopy, in the diagnosis and staging of endometriosis.

8. SUBJECTS AND METHODS

8.1 STUDY DESIGN

This is a protocol designed for a cross-sectional study with retrospective collection of data in order to compare the detection of Endometriosis by MRI combined with an AI program and laparoscopy.

MRI previous to laparoscopic procedures for the diagnosis of endometriosis will be recovered and re-analysed by an AI system. Hospital Universitari Dr. Josep Trueta (Girona) and Hospital de Santa Caterina (Salt) will participate in the study.

8.2 STUDY POPULATION

The chosen population includes patients diagnosed with endometriosis by laparoscopy during the years 2005-2021 in the province of Girona.

A retrospective search will be performed in the surgical pathology database for all confirmed cases of endometriosis between the years 2005-2021. Only women with a pathological diagnosis of endometriosis who underwent laparoscopy staging and had a pelvic MRI with adequate protocol will be considered for the study.

8.2.1 INCLUSION CRITERIA

- Women diagnosed with endometriosis with MRI imaging study previous to the laparoscopic procedure.
- Women who have signed the informed consent.

8.2.3 EXCLUSION CRITERIA

- Women with no MRI images available previous to the laparoscopic procedure.

8.3 SAMPLE

8.3.1 SAMPLE SIZE

No similar studies were found to make the sample calculation. For this reason, we have considered the study as a pilot study.

In a bilateral test, with alpha equal to 5%, statistical power of 80%, specificity of the laparoscopy equal to 79,23% (26) and the specificity of the MRI plus the AI analysis system, at least as 77%, specificity of the MRI (24), we would need 28 subjects taking into account 15% losses and 24 without any losses.

Computations carried out with the formula in Machin et al (40):

$$N = \frac{\left\{Z_{1-\alpha/2}\sqrt{[\pi_1(1-\pi_1)]} + Z_{1-B}\sqrt{[\pi_2(1-\pi_2)]}\right\}^2}{\delta^2}$$

8.3.2 SAMPLE SELECTION

Sample recruitment will be performed with a non-probabilistic sampling method. MRIs of all patients diagnosed with endometriosis in the province of Girona during a 10-year period (2005 -2021) and who have signed the informed consent will be recovered and re-analysed by the AI system.

8.4 VARIABLES

As this is a cross-sectional study, there are no dependent or independent variables. Nonetheless, we can define a main variable and covariables (Table 4) that influence the study.

8.4.1 MAIN VARIABLE

The main variable is the capacity of the AI analysis system combined with MRI to detect endometriosis.

8.4.2 COVARIABLES

- **Patient's age:** which is a continuous quantitative variable. It will be measured by the age of the participants at the moment of diagnosis.
- **Patient's symptoms:** presence of symptoms such as dyschezia, dyspareunia, noncyclic pain, chronic pelvic pain and gastrointestinal symptoms. Will be classified as dichotomic quantitative variable. It will be classified as 0 absence and 1 present.
- **Grade of endometriosis:** this is a quantitative discrete variable. It will be classified according to the rASM classification based on the laparoscopic findings in Stage 1 (minimal), Stage 2 (mild), Stage 3 (moderate), Stage 4 (severe).
- **Anatomic location of endometriosis:** which are qualitative variables, they are going to be classified as SUP, OMA or DIE as 1, 2 or 3 respectively. These variables will be classified depending on MRI findings:
    - 1. SUP: Endometriotic lesions, Deep or superficial, located at any site in pelvic/abdominal cavity on: peritoneum, fallopian tubes, ovaries, uterus, bowel, bladder or Pouch of Douglas
    - 2. OMA: Ovarian cysts lined by endometrial tissue (endometriomas)
    - 3. DIE: deep endometriotic lesions extending more than 5mm under the peritoneum located at any site of pelvic/ abdominal cavity. Subtypes of deep endometriosis per anatomical localisation are also going to be described, they will be subclassified as:
        - 3.1 Posterior DIE: Deep endometriotic lesions involve $\geq$ 1 site of the posterior pelvic compartment (USL, RVS, vaginal wall, bowel) and / or obliterate POD.
        - 3.2 USL endometriosis: Endometriotic lesions infiltrating the uterosacral ligaments unilaterally or bilaterally.
        - 3.3 RVS endometriosis: Deep endometriotic implants infiltrating the retroperitoneal area between the posterior wall of vaginal mucosa and anterior wall of rectal muscularis.
        - 3.4 Vaginal endometriosis: Endometriotic lesions infiltrating the vaginal wall, particularly posterior vaginal fornix.

- 3.5 POD obliteration: defined when the peritoneum of the POD is only partially or no longer visible during surgery, and occurs as a result of adhesion formation.
- 3.6 Bowel endometriosis: endometriotic lesions infiltrating at least the muscular layer of the intestinal wall ileum-rectum.
- 3.7 Rectosigmoid endometriosis: Endometriotic lesions infiltrating at least the muscular layer of the rectosigmoid colon.
- 3.8 Anterior DIE: deep endometriotic lesions located at any site of the anterior pelvic compartment which involves the bladder and anterior pouch.

All image variables are going to be characterized by signal intensity (high, low, or isodense to adjacent muscle) on unenhanced T1 weighted sequences.

Table 4. Covariables

COVARIABLES	Type of data	Measure instrument	Categories or values
AGE	Continuous quantitative	Clinical history	Number of years
SYMPTOMS	Dichotomic quantitative	Clinical history	0: Absence 1: Present
GRADE OF ENDOMETRIOSIS	Quantitative discrete variable	Clinical history	Stage 1: minimal Stage 2: mild Stage 3: moderate Stage 4: severe
ANATOMIC LOCATION	Qualitative variables	MRI findings (High, low or isodense)	1: SUP 2: OMA 3: DIE (3.1-3.8)

8.5 MEASURE INSTRUMENTS

8.5.1 MRI ANALYSIS

All MRI data sets will be reviewed by an expert radiologist using commercial image viewing software (Starviewer, Gilab, University of Girona; Girona, Spain). All the available MRI sequences will be reviewed: axial T1- weighted sequence; axial and sagittal fat-supressed fast spin-echo T1-weighted sequences; and axial, oblique coronal and sagittal T2-weighted sequences.

Criteria for MRI diagnosis of endometriosis consist; T2-weighted dark plaques, with or without high-signal-intensity foci on T1-weighted or fat suppression T1-weighted MRIs, corresponding to haemorrhagic foci or small hyperintense spaces on T2-weighted imaging within the different locations in the pelvis(41).

8.5.2 AI SYSTEM ANALYSIS

In order to proceed with this study, an AI analysis system has to be created. The system will consist of two different algorithms (*Figure 7 and 8*). The first one will be capable of classifying endometriosis in one of the three types (SUP, OMA or DIE) from given information provided by clinical and MRI image data of patients' records.

For this first step images have to be previously classified with their clinical variables: age, clinical symptoms and grade of endometriosis then a radiologist will have to describe the MRI of the patients. Once the images are classified, we will proceed into training the algorithm with a 29+1 system. This procedure consists of machine learning where the algorithm gets the information of 29 of the 30 MRIs that have already been described and paired with their clinical information. Once the system has been trained the 30th MRI is processed by the AI analysis system and classifies the image. This procedure will be repeated 30 times for each MRI.

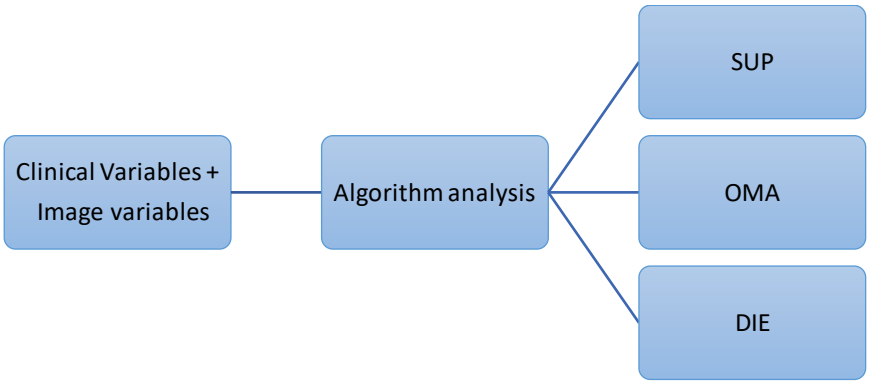

Figure 7. Algorithm I of the AI analysis System.

Once we obtained the results, we will compare them with the previous laparoscopic results in crosstabs.

If this first algorithm proves to work correctly, by classifying each MRI to the type of endometriosis described by the radiologist, we will proceed into creating the second algorithm.

The second algorithm learns through semi automatised segmentation method where a radiologist has to previously define the area that wants to be studied. For example, delimitation of the pelvis and then the AI analysis detects endometriosis based on the previously given variables. Since this second algorithm works as a first diagnostic step for the previously mentioned algorithm it has to give information about the localization and extension of endometriosis therefore the first algorithm can classify the information and diagnose the type of endometriosis.

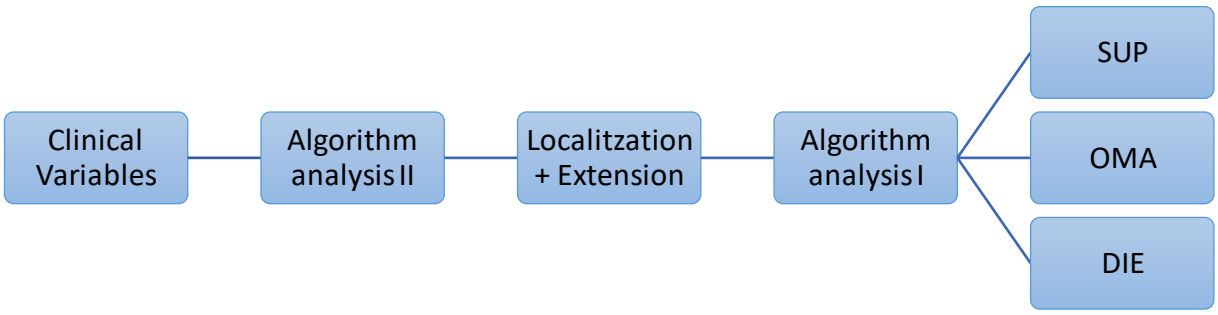

Figure 8. Algorithm II of the AI analysis System.

8.6 DATA COLLECTION

Data collection will consist in recovering patients' information that is already registered as this study is based on retrospective data. Clinical records will be extracted from the SAP and imaging data will be obtained from the Picture Archiving and Communication System (PACS).

- **Clinical records:** patients' information during the laparoscopic procedure will be extracted from their clinical records. Patient's age, patient's symptoms such as dyschezia, dyspareunia, noncyclic pain, chronic pelvic pain and gastrointestinal symptoms
- **MRIs:** MRIs from all patients will be recovered and classified by the radiologist according to the variables needed to enter the data into the AI analysis system.

9. STATISTICAL ANALYSIS

9.1. DESCRIPTIVE ANALYSIS

We will summarize all the qualitative variables using proportions and the quantitative variables using the mean, standard deviation, median and interquartile range.

We will stratify these descriptives by the type of endometriosis.

9.2. BIVARIATE INFERENCE

The difference of proportions of the qualitative variables (image – anatomic location) between the different types of endometriosis will be tested using the chi-square (x^3) or the Fisher's exact test (in case that in any cell the expected number was lower than 5).

The difference of means of the continuous quantitative variables (age, symptoms and grade) will be tested by the Student's test. The difference of the medians using the Mann-Whitney's test.

Once we obtained the results, we will compare them with the previous laparoscopic results using also an x^3.

9.2. VALIDITY OF THE AI

MRI detection rate for lesions is going to be calculated as the number of lesions detected by MRI, divided by the number of lesions detected at laparoscopy.

The validity of a test indicates the degree to which the investigator can get the assurance that the study conclusions are error free or accurate. It can be divided in:

- **Internal validity:** it is the extent to with the observed results represent the truth in the population that we are studying. It depends on the sensitivity and the specificity of the test.

$$Sensibility = \frac{True\ positives}{True\ positives + false\ negatives}$$

$$Especificity = \frac{True\ negatives}{True\ negatives + false\ positives}$$

- **External validity:** it is the extent to which the observed results can be applied outside the context of the study. It depends on the positive predictive value (PPV) and the negative predictive value (NPV), computed using the Bayes' theorem:

$$PPV = \frac{S \times P(Disease)}{S \times P(Disease) + (1-E) \times \{1-P(Disease)\}}$$

$$NPV = \frac{Ex\{1-P(Disease)\}}{E \times \{1-P(Disease)\} + (1-S) \times P(Disease)}$$

Once the results are given by the AI analysis system, they will be recorded in a contingency table considering the result of the test positive when the program detects each type of endometriosis. This step will be repeated for each type of endometriosis, see *tables 5, 6 and 7*.

The result '*NO ENDOMETRIOSIS'* is not possible as all the MRIs studied by the AI analysis system are positive for endometriosis. Therefore, if we gave the program the capacity of diagnosing the MRI as absent endometriosis we would be misleading the algorithm and the sensitivity and specificity of the diagnostic tool would not be calculated correctly. That is why we compared each subtype of endometriosis in order to classify the results in true positives, true negatives, false positives or false negatives.

Table 5. Study results of SUP's diagnosis.

		Laparoscopy		
		SUP	OMA	DIE
Artificial Intelligence	**SUP**	True Positives	False Positives	False positives
	OMA	False Negatives	True negatives	True negatives
	DIE	False Negatives	True negatives	True negatives

Table 6. Study results of OMA's diagnosis.

		Laparoscopy		
		SUP	**OMA**	DIE
Artificial Intelligence	SUP	True Negatives	False Negatives	True Negatives
	OMA	False Positives	True Positives	False Positives
	DIE	True Negatives	False Negatives	True Negatives

Table 7. Study results of DIE's diagnosis.

		Laparoscopy		
		SUP	OMA	**DIE**
Artificial Intelligence	SUP	True Negatives	True Negatives	False Negatives
	OMA	True Negatives	True Negatives	False Negatives
	DIE	False Positives	False Positives	True Positives

Once this step is done, the validity of the AI program system + MRI will be calculated and compared to the Gold Standard.

Secondary measurements will be performed, as well as the positive and negative likelihood ratio. They indicate the probability of a test being positive in patients suffering from the illness in respect to those who do not suffer from the illness and the probability of a test being negative in the same scenario, respectively.

$$RV+ = \frac{P(T+|Illness)}{P(T+|No\ Illness)}$$

$$RV- = \frac{P(T-|Illness)}{P(T-|\text{No } Illness)}$$

10. ETHICAL AND LEGAL CONSIDERATIONS

This protocol is going to be reviewed by the **Clinical Research Ethics Committee (CEIC)** of all the Hospitals participating in the study and their approval must be obtained before initiating the study.

Patient's autonomy is going to be respected according to the " *Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica"*. Before including patients in the study, they will receive an information document that will explain to them the procedures and meaning of the study (*Annex 3*). Prior to the recuperation of patients' data, written informed consent (*Annex 4*) must be signed by the patient.

Patients' personal data will be confidential according to the "*Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos"* and the "*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales*".

In order to maintain patients' privacy each of them will receive a numeric code for identification and personal identity and medical information will be maintained private. Data of the patients will only be available for the Research team and Ethical and Clinical Investigation Committee.

Finally, investigators will declare they have no conflicts of interest in any aspect of the study.

11. STUDY STRENGTHS AND LIMITATIONS

Strengths of this study should be taken into account:

- As this protocol describes a cross-sectional study with a retrospective collection of the data, MRI images are already taken, therefore the study will take less time to perform and will be less expensive. Rather than performing a prospective design.
- No ethical difficulties, meaning that as MRI images are already taken, patients do not need to undergo any procedure.
- As samples are already collected, there can be no patient loss because of the sampling method.

Nonetheless, several limitations of this study also need to be acknowledged:

- The results will be obtained from two hospitals and might not extrapolate to other centres because of the small size of the sample. However, the present study might serve for a future multicentric study that would allow performing more precise estimations.
- As the collection of data for the study is done retrospectively some covariables might not be collected if there is a lack of information in the medical history records.
- As this is a transversal study with retrospective data some MRI images might not have been acquired with the nowadays standard protocol therefore image resolution might not be the perfect fit. Therefore, we can expect a measurement bias. Nonetheless, we expect the AI algorithm to minimize the differences.
- The high cost of this project can also be considered a limitation.
- The sample selection for this study is done as non-probabilistic recruitment, so a selection bias has to be taken into account, a multicentric study including other hospitals of Catalonia should be done.

12. WORK PLAN AND CHRONOGRAM

Two hospitals are going to participate in the study: Hospital Universitari Doctor Josep Trueta (Girona) and Hospital de Santa Caterina (Salt).

The research team will be composed by:

- **1 general coordinator of the study and a co-investigator** will take care of the elaboration of the protocol and will be in charge of the study. They will also be in charge of the data recollection from the study and present them to the statistician.
- **1 Software engineer in DEEP learning** who will be in charge of creating the AI analysis system and will take care of all the learning algorithm process.
- **1 Ph.D. in DEEP learning** who will evaluate the AI analysis system.
- **1 Radiologist** from Hospital Josep Trueta who will analyse all the MRIs for the first part of the algorithm.
- **1 Statistician** from the Institut d'Investigació Biomèdica de Girona (IdibGi) who will perform the statistical analysis.

This study will last about 15 months, from November 2021 to January 2023 divided into 7 phases (*table 8*).

1. **Protocol elaboration (November 2021 – January 2022)**

   Protocol elaboration will be the first item presented. During this first step hypothesis, objective and protocol of the study will be designed. Research of information and resources will be done in order to create an adequate protocol.

2. **Ethical evaluation (February 2022)**

   Ethical evaluation will take place in the second phase of the study. Both centres involved in the study will discuss the protocol with their ethics board for its final evaluation and approval.

3. **Information to participants and informed consent (March 2022)**

   All participants that meet the inclusion criteria for the procedure of our protocol will be contacted and provided with the information sheet. Only participants who have signed the informed consent after reading all the information will be part of the study.

4. **MRI recovery (April 2022 – June 200)**

   Patients' MRIs will be recovered from the PACS system and will be re-avaluated by our radiologist. The radiologist will classify each image into the variables explained in the Variables section.

5. **MRI reassessment by AI analysis (July 2022 – August 2022)**

   All MRIs will be introduced in the base of the AI analysis system and all the images will be evaluated by the system. First for Algorithm nº1 and then for algorithm nº1 + nº2.

6. **Data analysis (September 2022 – October 2022)**

   Statistical analysis will be performed by a specialized statistician. Results will be presented in tables and conclusions will be written by the investigators.

7. **Publication of results (November 2022 – January 2023)**

   The study's results will be written in an article that will be further edited and published.

Table 8. Chronogram

STUDY PHASES	2021		2022												2023
	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J
PROTOCOL ELABORATION															
ETHICAL EVALUATION															
INFORMED CONSENT															
MRI RECOVERY															
MRI REASSESSMENT BY AI ANALYSIS															
DATA ANALYSIS															
PUBLICATION OF RESULTS															

13. BUDGET

MATERIAL COSTS:

- Informed consent sheet: for a sample size of 30 patients, we will print 30 information sheets and 30 informed consent double-sided sheets at 0,10€ per copy with a total of 6,0€.
- Computer with GPU: in order to create the AI analysis program a computer with GPU is required. It will cost 5.000€.

PERSONNEL COSTS:

- Software engineer with DEEP learning knowledge who will create the AI analysis program and take care of the process throughout all the study. For 25€/h and working approximately 100h in a month and for two months, it will cost 5.000€.
- Ph.D. in DEEP learning knowledge 30€/h for 30h in a month and for two months, who will supervise the whole project of creating the AI analysis system, it will cost 1.800€.
- Qualified statistician from Institut d'Investigació Biomèdica de Girona (IdibGi) who will carry out the statistical analysis. For 30€/h and working 65h in a month for two months, will cost 3.900 €.
- Radiologist from Hospital Josep Trueta who will carry out the MRI analysis. For 30€/h and working for 50h in a month for three months, it will cost 4.500€.

DIVULGATION COSTS:

- Publication fees: 1.000€ to publish in a journal article
- Inscriptions to congresses: 800€ for national congresses attendance and 1.600€ for international congresses attendance.

See budget at table 9.

Table 9. Budget

	Point	Cost	Total
Materials	Information and consent sheet (60 copies)	0,10€/copy	6,00€
	Computer with GPU	5.000€	5.000€
Personnel	Software engineer with DEEP learning knowledge	25€/h	5.000€
	Ph.D. in DEEP learning knowledge	30€/h	1.800€
	Statistician	30€/h	3.900€
	Radiologist	30€/h	4.500€
Divulgation costs	Publication fees	1.000€	1.000€
	Inscription for congress	800€ + 1.600€	2.400€
			23.606€

14. FEASIBILITY

This study will be performed by expert radiologist with more than 15 years reading female pelvic MRI examinations. The PACS and SAP systems are a structured database where all clinical information and imaging studies of a patient can be uploaded with all the data required for the study.

Development of the artificial intelligence algorithms will be performed by experienced engineers from the The Institute of Computer Vision and Robotics Research (ViCOROB) at the University of Girona. ViCOROB is a leading institute in Catalonia in the areas of: Medical image analysis, multimedia image analysis and artificial intelligence. Previous research and development of AI analysis systems and its algorithms have been developed from ViCOROB on breast and prostate cancer diagnosis.

The main limitation in the execution of this protocol is the number of MRIs available and the cost of the AI analysis system. Nevertheless, we believe in its technical feasibility and in research scholarships to make it possible.

15. CLINICAL AND HEALTHCARE IMPACT

Despite a range of symptoms, diagnosis of endometriosis is often delayed due to a lack of non-invasive, definitive tools for the diagnosis of endometriosis.

If the hypothesis of this study is validated by the results, it would be reasonable to contemplate a change in the current image diagnosis of endometriosis, especially in pre-surgical planning.

With favourable results, patients could benefit from a hybrid technique that can enable them into taking a more informed decision and also empower surgeons by improving their surgical plan and giving them more information about the depth and extension of the endometriosis.

In addition, the AI system can provide expert-guided imaging that lacks in centres where there are no specialised radiologists in endometriosis.

Thus, the final potential benefit could be improving the management of endometriosis. Developing a more consistent handling of such complex disease would show a significant change in all different steps of its management from early diagnosis, better treatment and all the significant related social, public health and economic implications.

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17. ANNEXES

Annex 1. American Society for Reproductive Medicine Revised Classification of Endometriosis.

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date_____

Stage I (Minimal): 1-5
Stage II (Mild): 6-15
Stage III (Moderate): 16-40
Stage IV (Severe): >40
Total: _____

Laparoscopy_____ Laparotomy_____Photography__
Laparoscopic Treatment_____
_____
Prognosis_____

PERITONEUM	ENDOMETRIOSIS	<1cm	1-3 cm	>3 cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20

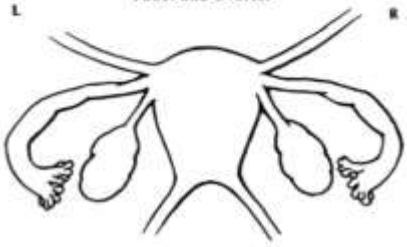
	POSTERIOR CULDESAC OBLITERATION	Partial	Complete
		4	40

OVARY	ADHESIONS	< 1/3 Enclosure	1/3-2/3 Enclosure	> 2/ 3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBES	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

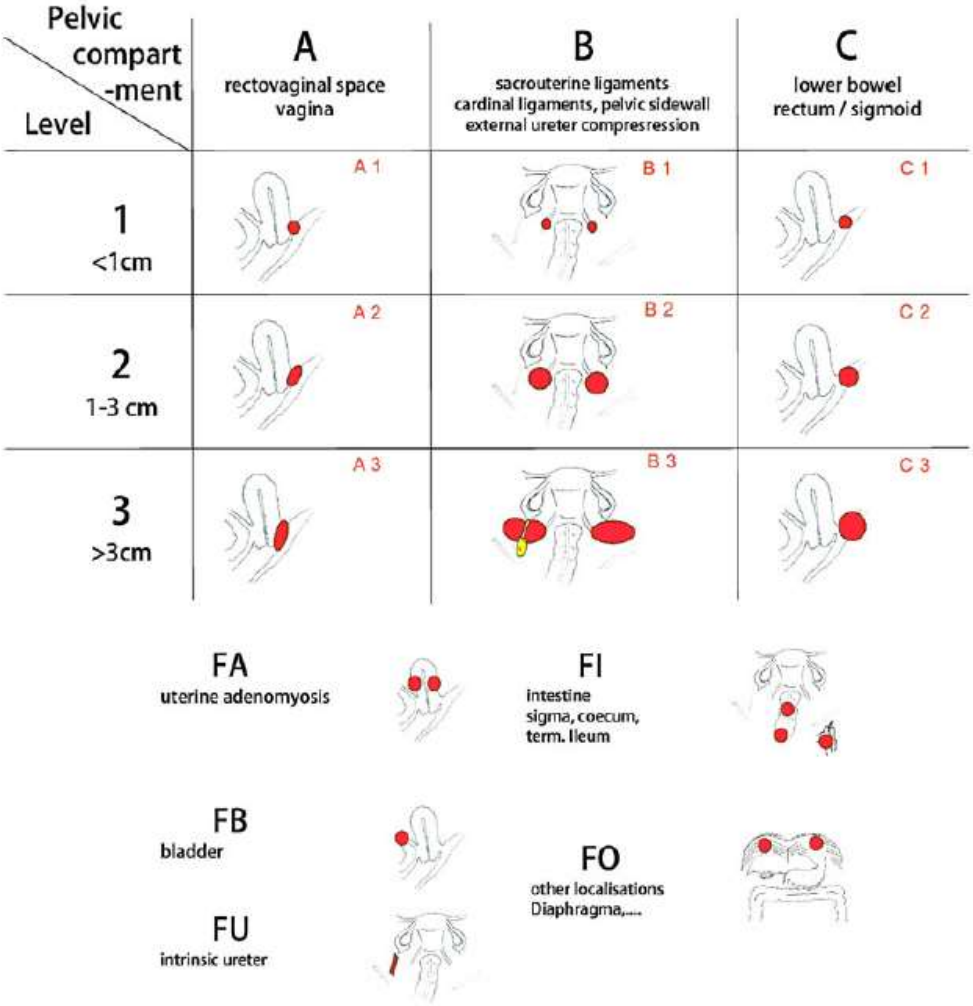
Additional Endometriosis:_____ Associated Pathology:_____

To Be Used with Normal Tubes and Ovaries



To Be Used with Abnormal Tubes and Ovaries

Annex 2. Enzian Classification



Annex 3. Information Sheet

FULL D'INFORMACIÓ AL PACIENT

AVALUACIÓ DE LA COMBINACIÓ DE LA RMI AMB INTEL·LIGÈNCIA ARTIFICIAL EN EL DIAGNÒSTIC DE L'ENDOMETRIOSI.

INVESTIGADORS PRINCIPALS: Dr. Kai Vilanova Busquets i estudiant Júlia Cano i Serrat.

INTRODUCCIÓ:

Ens dirigim a vostè per informar-la sobre un estudi en el que està convidada a participar que es realitzarà amb la participació de pacients provinent de l'Hospital Dr. Josep Trueta de Girona i l'Hospital de Santa Caterina de Salt. Aquest full informatiu pretén fer-li arribar tota la informació necessària perquè vostè decideixi si vol o no participar en l'estudi. Llegeixi atentament la informació proporcionada i consulti en cas de tenir qualsevol dubte.

OBJECTIU DE L'ESTUDI:

Aquest estudi té com a principal objectiu avaluar la utilitat de la Ressonància Magnètica conjuntament amb un programa d'intel·ligència artificial en el diagnòstic de l'endometriosi.

PARTICIPACIÓ DE LES PACIENTS EN L'ESTUDI:

L'estudi es conduirà de manera observacional a partir de dades ja gravades en el nostre sistema per la qual cosa vostè no haurà de ser sotmesa a cap prova. Es pretenen avaluar els resultats de la Ressonància Magnètica abdomino-pèlvica que se li va realitzar abans de ser sotmesa a un procediment quirúrgic a causa de l'endometriosi. També volem recollir algunes dades de la seva història clínica relacionades amb la seva malaltia.

PARTICIPACIÓ VOLUNTÀRIA:

La seva participació en aquest estudi és totalment voluntària. En cas que decideixi no participar les seves dades no es tindran en compte en cap moment i no li suposarà cap perjudici en un futur. En tot moment durant l'estudi vostè té el dret a revocar el seu consentiment.

CONFIDENCIALITAT:

La informació recollida en aquest document serà totalment confidencial segons el "*Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, del 27 de abril de 2016, relativo a la protección de las persones físicas en lo que repecta al tratamiento de datos personales y a la libre circulación de estos datos",* i la *"Ley Orgánica 3/2018 de 5 de diciembre, de Protección de Datos Personales y garantia de los derechos digitales"*. La informació serà emmagatzemada en una base de dades anònima.

En cas de publicació de resultats a través de publicacions i/o congressos les seves dades seran tractades de forma anònima.

Annex 4. Consent sheet

DOCUMENT DE CONSENTIMENT INFORMAT PER A:

Investigadors principals: Dr. Kai Vilanova Busquets i estudiant Júlia Cano i serrat.

Manifesto que:

1. He llegit i entès el full informatiu sobre l'objecte de l'estudi.
2. He tingut l'oportunitat de fer preguntes.
3. Les meves preguntes s'han respost satisfactòriament.
4. He rebut prou informació de l'estudi.
5. Entenc que la participació és voluntària.
6. D'acord amb el que estableix el reglament (UE) 2016/679 del Parlament Europeu i del Consell, de 17 d'abril de 2016, relatiu a la protecció de les persones físiques pel que fa al tractament de dades personals i a la lliure circulació d'aquestes dades i la Llei Orgànica de Protecció de Dades de Caràcter personal i Garantia dels Drets Digitals (3/2018), m'han informat que les meves dades personals, obtingudes per haver emplenat aquest formulari, i les dades resultants de la meva participació en el projecte es tractaran sota la responsabilitat de l'Hospital Josep Trueta per tal de gestionar la meva participació en aquest projecte de recerca. A més, m'han informat sobre els següents aspectes:
    - Que està previst elaborar perfils per analitzar aspectes sobre la meva salut.
    - Que les meves dades personals, obtingudes per haver emplenat aquest formulari, i les dades resultants de la meva participació en el projecte es conservaran anònimes durant tot el procés. En qualsevol cas, no es poden cedir sense el meu consentiment exprés, que no atorgo en aquest acte.
7. Estic d'acord que el meu consentiment per escrit i altres dades estiguin a disposició del projecte de recerca en què participo i a disposició de Kai Vilanova (investigador responsable) i Júlia Cano (estudiant) però sempre respectant la confidencialitat i la garantia que les meves dades no estaran disponibles públicament de manera que se'm pugui identificar.

8. Signo aquest document d'informació i consentiment de manera voluntària per manifestar el meu dret de participar en aquest estudi de recerca. Rebo una còpia d'aquest document per guardar-lo i poder consultar-lo en un futur.

Nom i cognoms de la pacient: .....

DNI/ passaport:.....

Signatura:..... Data:.....

Nom i cognoms de l'investigador: .....

Nº de col·legiat: .....

Signatura:..... Data:.....