Are pain symptoms related to endometriosis location?

PROTOCOL TITLE: *Are pain symptoms related to endometriosis location?*

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Sponsor	Project will be submited to funding

Pain and endometriosis *Pain and endometriosis location*

PROTOCOL SIGNATURE SHEET

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

EXAMPLES

rASRM	*revised American Society for Reproductive Medicine*
LARS	*Lower anterior rectum syndrome*
FSFI	Female Sexual Function Index
EHP-30	*Endometriosis health profile questionnaire- 30*
MRI	*Magnetic ressonance imaging*

LIST OF FIGURES

Resumo

A endometriose afeta cerca de 10–20% das mulheres em idade reprodutiva e define-se pela presença de glândulas e estroma semelhantes ao endométrio fora da cavidade uterina. Está associada a dor, com impacto significativo na qualidade de vida e potencial compromisso da fertilidade. Vários estudos demonstram que a intensidade da dor não se correlaciona diretamente com o estádio da doença. A endometriose pode ser descrita pela classificação revista da American Society for Reproductive Medicine (rASRM) ou pela classificação ENZIAN, utilizada também na avaliação por ressonância magnética. O envolvimento intestinal, nomeadamente do cólon e reto, associa-se a sintomas intestinais, embora a evidência mais recente não demonstre que lesões localizadas mais próximas do ânus estejam associadas a maior intensidade sintomática. Além disso, diferentes localizações de endometriose apresentam desfechos cirúrgicos distintos, sendo a endometriose da parede abdominal associada a melhores resultados cirúrgicos do que a endometriose pélvica, com menor dor, menor taxa de recidiva e menos complicações.

Este estudo prospetivo observacional tem como objetivo principal avaliar a correlação entre os padrões de dor e a distribuição anatómica da endometriose profunda. Como objetivos secundários, pretende-se comparar a relação entre as queixas das doentes e a descrição ENZIAN obtida por ressonância magnética com a classificação ENZIAN cirúrgica, caracterizar as doentes com endometriose reto-sigmoide avaliando se a proximidade do nódulo ao ânus se associa a maior intensidade dos sintomas, e descrever a evolução dos sintomas antes e após a cirurgia em diferentes grupos de doentes, explorando se a localização da endometriose influencia a evolução da dor e os desfechos clínicos.

Serão incluídas todas as mulheres com endometriose propostas para cirurgia, com idade igual ou superior a 18 anos, excluindo-se as doentes sem confirmação histopatológica de endometriose, pós-menopáusicas, com idade superior a 55 anos ou com idade inferior a 18 anos. O estudo terá a duração de 24 meses. Serão avaliadas as características das doentes, incluindo idade, história obstétrica, infertilidade, índice de massa corporal e uso de contraceção, bem como as queixas dolorosas (dismenorreia, dispareunia, disquézia, disúria e dor pélvica crónica), a função sexual, a qualidade de vida (EHP-30) e a sintomatologia retal, através do questionário LARS. A descrição anatómica cirúrgica será realizada segundo a classificação ENZIAN, incluindo a distância das lesões ao ânus e a permeabilidade tubária. A evolução clínica após a cirurgia será avaliada através dos mesmos questionários, da análise de complicações cirúrgicas e de um questionário de fertilidade. A recolha de dados será efetuada antes da cirurgia, até um mês previamente, e no seguimento aos 6 meses, 1 e 2 anos após a intervenção cirúrgica, permitindo a avaliação longitudinal da evolução dos sintomas.

SUMMARY

Purpose and rationale:

Endometriosis affects 10-20% of women in reproductive age (1). The disease is defined by the presence of endometrial-like glands and stroma outside the uterine cavity (2). Is associated with pain, affecting the quality of life and, potentially, affecting fertility (3). Several studies have concluded that the severity of the pain does not correlate with the disease stage. The description of endometriosis could be done using the revised American Society for Reproductive Medicine (rASRM) score, or the ENZIAN classification that is also used in MRI description (4). Endometriosis affecting bowel and rectum is associated with bowel related symptoms (5); recent evidence does not show that endometriosis closer to anus is associated with more intense symptoms (6). Finally, not all endometriosis has the same surgical outcome, for example, abdominal wall endometriosis (7) seems to have a better surgical outcome than pelvic endometriosis with less pain and recurrence rate after surgical treatment, with less complications.

Primary objective: *correlation between pain patterns and anatomical distribution of deep endometriosis*

Secondary objective:

- *to compare if the MRI ENZIAN description is more related to patient complains comparing it with surgical ENZIAN classification.*
- *to describe the characteristics of patients with recto-sigmoid endometriosis evaluating the possibility that patients with endometriosis nodule closer to the anus have more symptoms intensity;*
- *to describe the evolution of symptoms before and after the surgery between different endometriosis patients' groups exploring the idea that different endometriosis location has different pain evolution /outcomes*

Study type: *prospective*
Study design: *prospective observational*
Study population: *every woman who is proposed for endometriosis surgery*
Key inclusion criteria: *patients with endometriosis proposed for surgery; patients with 18 years or older*

Key exclusion criteria: *patients proposed for endometriosis surgery that had no histopathological confirmation of endometriosis in surgical specimen; after menopause or after 55 years old; younger than 18 years old.*

Study duration: *24 months.*

Main study parameters/endpoints:

Patient characteristics – age; number of previous pregnancy; history of infertility; BMI; use of contraceptive
Pain complains: dysmenorrhea; dyspareunia; dyschesia; dysuria; chronic pelvic pain in NRS.
Patient evaluation in sexual function
Patient evaluation in quality of life EH-30
Patient evaluation in rectal symptomatology - Lower anterior rectum syndrome (LARS)

Patients' surgical anatomical description (ENZIAN); distance to anus; tubal permeability.

Patients' evolution after surgery with previous questionaries and surgical complication questionnaire. Fertility questionnaire.

Data analysis:
Data will be collected before surgery – 1 month before.
Data will be fulfilled by surgeon with ENZIAN and rASRM classification of each surgery. And distance to anus. And
Data will be collected 6 months 1 and 2 years years after the surgery to check patients evolution.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

No relevant burden or risks for the participants – observational design.

The idea of describing better specific types of endometriosis will eventually lead physicians to recognise easier specific types of endometriosis and, diagnose and treat them earlier.
In the group of patients with rectal and sigmoid endometriosis the description of patients complains may reveal that disease closer to the anus may be associated with more intensity complains. We

already know that these patients are at high risk of complication (rectal leakage); now we aim to find if patient´s location is associated with more complains and more complications.

Finally, the comparison of different type of endometriosis evolution after surgery is not well described. We hope to find that different locations have a lower recurrence and better evolution of pain after the surgery – specifically if abdominal wall/caesarean scar endometriosis has a better evolution /outcome after surgery than pelvic/rectovaginal endometriosis. This may help surgeons explain their surgeries to patients namely their expectations offering a more patient oriented approach with better and more accurate information.

INTRODUCTION AND RATIONALE

.1 Scope of the problem

Endometriosis is a disease defined by endometrial-like glands and stroma outside of the uterine cavity. It is. associated with pain and can affect fertility. Pain and patient´s complain are not, specific of a certain location. If we find different patient complains more specific to a certain location, we will have an easier diagnosis and potentially better access to proper treatment. There are several locations for endometriosis; different locations have a distinct prognosis after surgery. If we expand our information regarding this different prognosis we will have better information for patients.

.2 Summary of relevant literature

Endometriosis affects 10-20% of women in reproductive disease (8). The disease is defined by the presence of endometrial like glands and stroma outside the uterine cavity (9)]. Due to the difference in site, pathogenesis, and hormonal responsiveness, peritoneal, ovarian, and rectovaginal endometriosis can be considered as three distinct entities. Endometriotic lesions that infiltrate deeper than 5 mm under the peritoneum are considered deep endometriosis (10).

One of the challenges at present time is the preoperative staging of the disease. Unfortunately, clinical examination is insufficient to identify DIE lesions, especially in higher pelvic locations (11) . For the non-invasive diagnosis of endometriosis, accurate imaging techniques such as transvaginal ultrasound (TVS) or MRI are necessary (12).

As a result of destructive alterations at different sites produced by endometriosis, this disease is frequently associated with complex symptoms like dysmenorrhea, deep dyspareunia, chronic pelvic pain, and dyschezia. Several studies have concluded that the severity of the pain does not correlate with the disease stage (13) (14) (15). On the other hand, it has been observed that the severity of the pain correlates with the depth of infiltration (9) (16) .

Most studies describe endometriosis location using the revised American Society for Reproductive Medicine (rASRM) score, which does not take into account the involvement of retroperitoneal structures with DIE (17) . As an alternative, the ENZIAN classification that takes into account both the involvement of retroperitoneal structures and adenomyosis has been described (4) . We recently published a meta-analysis in this subject that concluded that rASRM score is not well correlated with patient complains (18).

The etiopathogenesis of the pain related to endometriosis is multifactorial: from local inflammatory mediators such as prostaglandins, histamine, kinins, and interleukins that eventually lead to pelvic

adhesions and spasticity of the pelvic floor muscles, to neurogenic inflammation due to the ingrowth of nerve fibers into endometriotic lesions and central sensitization translated as an exaggerated response to a normal stimulus (19) (20) (21) (22). The treatment of endometriosis should focus on symptom reduction and quality of life enhancement. Even though controversy reigns over the management of deep infiltrating endometriosis, there is a general consensus that all visible endometriotic lesions should be surgically removed completely while taking great care to minimize ovarian damage (23) (24) (25) [17–19]. Surgical outcomes of endometriosis have different success and recurrence rates depending on the location (7) (26).

In order to describe the relationship between endometriosis location and pain characteristics we need an accurate disease classification. Even if rASRM is the most used ENZIAN is a more anatomically accurate description of the disease (5). To quantify the pain burden, we need to use a numerical rating scale (NRS) or visual analog scale (VAS) because these instruments are tested, validated and widely used. Estimating the quality of life using only visual analog scales is very simple but inexact, thus highlighting the need for more complex tools of measurement. Of the many diseases specific tested and validated questionnaires, EHP-30 seems to be the best suited and validated for Portuguese language (27).

Rationale

We aim to describe pain and patient´s complains in different locations of endometriosis. According to the anatomical description of the endometriosis find if some type of pain or pain intensity are more specific to a single location.

Subgroup analysis of patients with rectal and sigmoid endometriosis will be done to describe if endometrial nodule closer to anus or larger dimension are more symptomatic.

Subgroup analysis will be done evaluating the accuracy of anatomical description of endometriosis in MRI in comparison to surgical description.

Finally, patients' evolution /outcomes after surgery will be measured to describe if different types of endometriosis have different evolution/prognosis.

STUDY OBJECTIVES AND END POINTS

Primary objective: *Correlation between pain patterns and anatomical distribution of deep endometriosis*

Secondary objective:

- *to compare if the MRI ENZIAN description is more related to patient complains comparing it with surgical ENZIAN classification.*
- *to describe the characteristics of patients with recto-sigmoid endometriosis evaluating the possibility that patients with endometriosis nodule close to the anus have more symptoms/ or higher intensity;*
- *to describe the evolution of symptoms before and after the surgery between different endometriosis patients' groups exploring the idea that different endometriosis location has different pain evolution / disease recurrence after the surgery.*
- *does MRI anatomical classification correlate with complications or surgical duration?*
- *does MRI classification correlate with anatomopathological results?*

INVESTIGATION PLAN

.3 Study design

This is a prospective observational cohort study. All patients with a confirmed diagnosis of endometriosis who are scheduled for elective surgery will be invited to participate.

Patients will first be assessed in consultation by a surgeon, who will determine the indication for surgery based on clinical criteria. Once surgery is proposed, the administrative team will process the surgical booking. If the endometriosis diagnostic code is included in the surgical request, the patient will be automatically flagged as potentially eligible for the study, using a universal selection approach.

Eligible patients will receive information about the advantages and disadvantages of participation from the surgeon and will be given access to the informed consent document. If they agree to participate, the informed consent form will be signed with the surgeon/investigator. A video consultation with patients who agree to participate will be scheduled to answer questions and clarify any issues if needed and/or requested. The signed consent form will be stored securely by the principal investigator. Upon confirmation of participation, an email will be sent with baseline questionnaires assessing pain, quality of life, fertility, and sexual function. These questionnaires will be collected through online tool, and administration will be carried out by professionals who will not have access to patients' identities or any personal data that could allow patient´s identification. A key number will be assigned to each patient to enable pseudonymization and data processing during the study. Only the principal investigator will have access to this key.

Postoperative follow-up will include additional online assessments at 6 and 12 months, and 2 years after surgery. If a patient prefers paper-based questionnaires, these will be provided upon request.

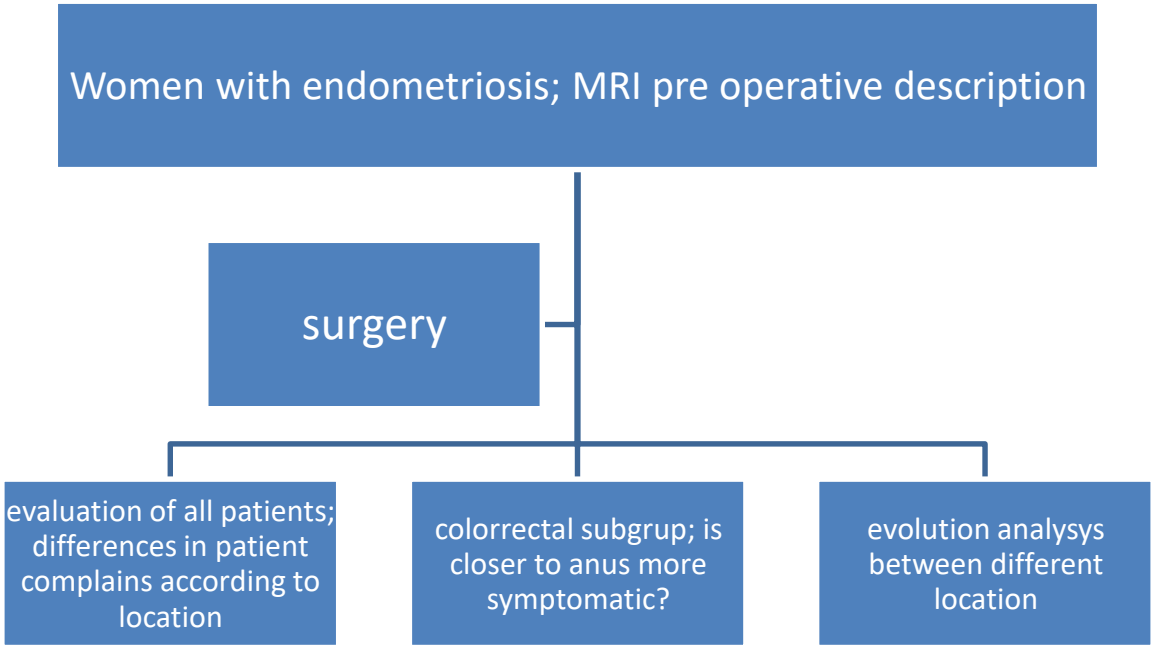

Figure 1- description of study

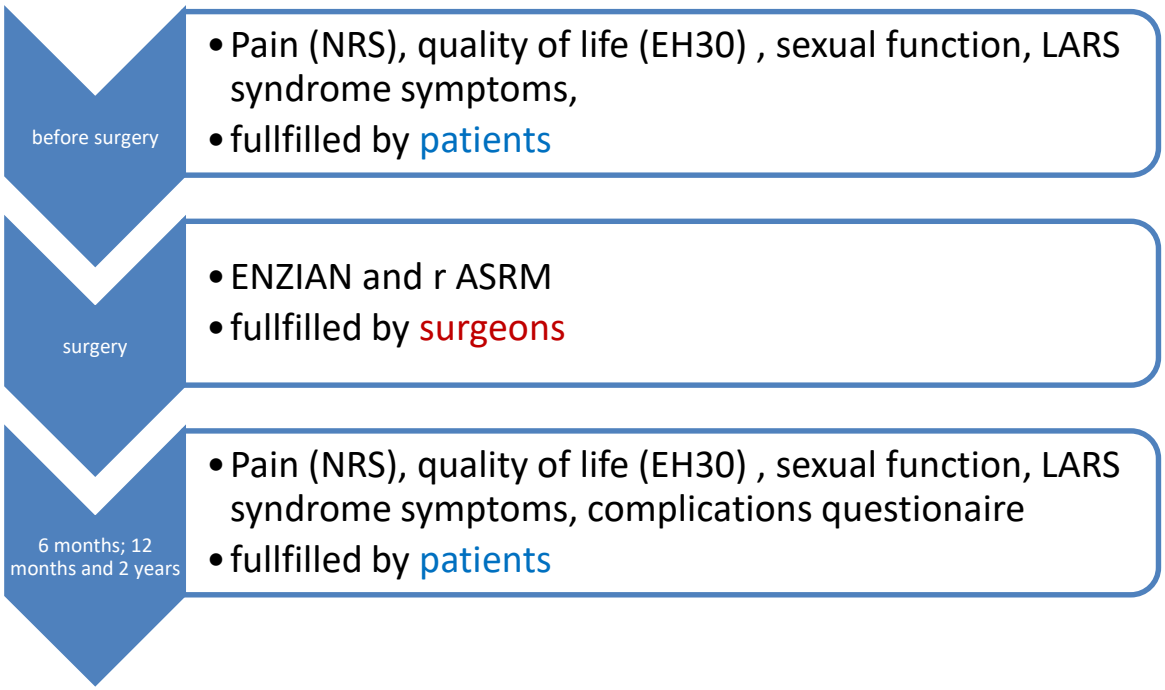

Figure 2: data collection timeline – to insert in web-based platform

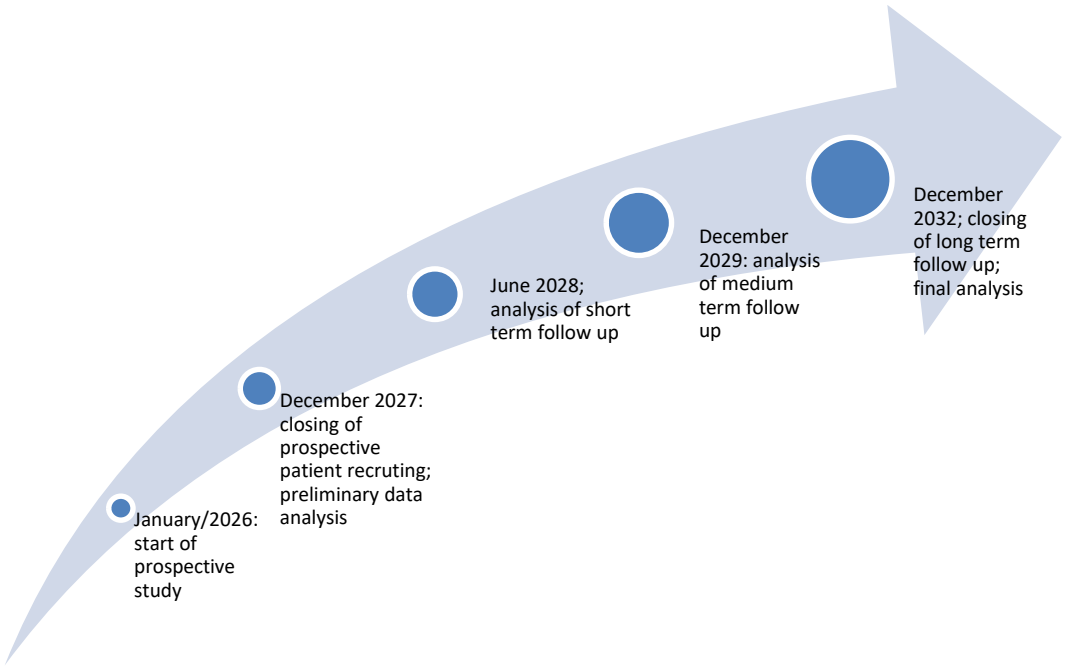

Figure 3: study calendar

.4 Rational for the study design

Easy to administer; patient fulfilled questionnaire with low burden for surgeons.

Because we are studding patient´s complains and relationship with disease location no need for a different design.

.5 Risks and benefits

No relevant burden or risks for the participants – observational design.

The idea of describing better specific types of endometriosis will eventually lead physicians to recognise easier specific types of endometriosis and, diagnose and treat them earlier.
In the group of patients with rectal and sigmoid endometriosis the description of patients complains may reveal that disease closer to the anus may be associated with more intensity complains. We already know that these patients are at high risk of complication (rectal leakage) so now we aim to find if patient´s location is associated with more complains and more complications.
Finally, the comparison of different type of endometriosis evolution after surgery is not described. We expect to find that different locations have a lower recurrence and better evolution of pain after

the surgery – specifically if abdominal /scar endometriosis has a better evolution /outcome after surgery than pelvic endometriosis.

STUDY POPULATION

.6 Source population

All patients who have surgery for endometriosis. (1) recruitment will be on the consultation followed by on line by e-mail before the surgery (2) expected to include 460 patients – 2 years (around 5-6 patients per week). We expect around 400 patients with rectovaginal endometriosis; 40 patients with bladder endometriosis; 40 patients with abdominal wall endometriosis and 20 patients with ureter endometriosis. We expect 80 patients with rectal/sigmoid endometriosis. In order to be able to compare we need a minimum of 30 per group to be able to drawn more accurate conclusions.

.7 Inclusion criteria

Female patients with endometriosis proposed for surgery

.8 Exclusion criteria

Patients proposed for endometriosis surgery that had no histopathological confirmation of endometriosis in surgical specimen; pregnant patient; younger than 18 years old or older than 50 years old.

METHODS

.9 Study parameters

Patient characteristics – age; number of previous pregnancies; history of infertility; BMI;

Pain complains: dysmenorrhea; dyspareunia; dyschesia; dysuria; chronic pelvic pain in NRS. (21)

Female Sexual Function Index (FSFI) tool (22)

Patient evaluation in quality of life EH-30 (23)

Patient evaluation in rectal symptomatology - LARS syndrome

Patients' surgical anatomical description (ENZIAN and rASRM)

Patients' evolution after surgery with previous questionaries (pain complains, sexual function, quality of life and rectal symptomatology) and surgical complication questionnaire (to be built based on clavien Dindo) and Global Improvement Score and fertility questionnaire.

Data analysis:

Data will be collected before surgery – 1 month before – by e-mail with secure web-based software platform questionnaire after patient acceptance.

Data will be fulfilled by surgeon with ENZIAN and rASRM classification of each surgery.

Data will be collected 6 months 1 and 2 years after the surgery to check patients' evolution.

.10 Study procedures

Data will be collected before surgery – 1 month before – by e-mail with secure web-based software platform questionnaire after patient acceptance.

Data will be fulfilled by surgeon with ENZIAN and rASRM classification after each surgery. Secure web-based software platform

Data will be collected 6 months 1and 2 years after the surgery to check patients' evolution.

SAFETY MONITORING

Observational study so no need for safety monitoring. In the unlikely event a patients died during the study she does not receive mail of follow up questionnaires and this is noted by research team.

DATA REVIEW AND DATABASE MANAGEMENT

.11 Handling and storage of data

Data will be stored in a secure web-based software platform

Data responsibility

Data access is limited to chief researcher.

- **STATISTICAL ANALYSIS**

Patient with rectovaginal endometriosis have a more frequent or severe dyspareunia?

Patient with bladder endometriosis have a more frequent/ dysuria intensity complains?

Patient with rectal endometriosis have a more frequent LARS symptoms – frequency / urgency/incontinence?

Patients with abdominal wall endometriosis have a better surgical outcome (less pain) compared with pelvic endometriosis?

Cofounders:
Surgeon a,b,c,….
Patient under oral contraceptive pill
Several locations of endometriosis in same patient

Continuous variables will be summarised using appropriate measures of central tendency and dispersion, and categorical variables will be presented as absolute and relative frequencies. Baseline demographic and clinical characteristics will be compared across location groups to explore potential differences that may act as confounders. For these comparisons, suitable statistical tests (analysis of variance or non-parametric alternatives for continuous data, and chi-square or Fisher's exact test for categorical data) will be applied. Graphical presentations of longitudinal follow-up data will be presented to describe the evolution of the main outcomes by location groups.
For each continuous outcome, multivariable linear regression models with robust standard errors will be fitted, with disease location encoded using the ENZIAN classification to allow for multi-site involvement. Semi-partial R^2 will quantify the variance in outcomes explained by disease location. Longitudinal changes in symptoms will be analysed using linear mixed-effects models. Estimates will be adjusted for socio-demographic (e.g., age) and clinical covariates (e.g. patient under oral contraceptive pill), and surgeon. For binary outcomes, logistic regression or generalized linear mixed models will be applied as appropriate. Results will be reported as adjusted mean differences with 95% confidence intervals. Normality of residuals (Q–Q plots) and homoscedasticity (residual-versus-fitted plots) will be evaluated.
Concordance between MRI and surgery ENZIAN will be assessed using Cohen's weighted kappa coefficient.
Missing data will be handled under a Missing at Random assumption using multiple imputation by chained equations. Sensitivity analyses will explore non-random missingness.

*The primary analysis compares chronic pelvic pain across the eight anatomical categories of the ENZIAN classification. A clinically relevant difference was defined as at least a 2- point change on the NRS between groups. Using standard assumptions for a medium effect size (Cohen´s f =0.25), a significance level of 5%, and 95% power, a one-way ANOVA with 8 groups requires a total of 360 participants (calculated using G*Power 3.1.9.6). Assuming a 20% dropout rate, a final sample size of 450 women is required.*

ETHICAL CONSIDERATIONS

.1 Regulatory and ethical compliance

The study will be conducted accordingly with the Helsinki Declaration, the good clinical practises and the Portuguese legislation.

.2 Recruitment and inform consent

Only individuals aged 18 years or older will be eligible to participate in the study. Participants with cognitive impairments will only be enrolled if informed consent is obtained from their legally authorized representative.
Recruitment will be done in the consultation with the surgeon without obligation. If patients quit study the standard of care is the kept.

.3 Benefits and risks assessment, group relatedness

It is clearly stated the risks and benefits of our study for patients. Because it is an observational study there are no clinical risks for the patients and the time spent fulfilling the questionnaires is the main setback for patients from our study. On the other hand, if we improve our understanding of the disease and its relationship between disease location and complains we main improve the diagnostic accuracy and have a patient-oriented perspective that may help us understand why different patients have different complains with apparently similar disease (Vercellini, Facchin et al. 2018). It is also clear that during the study each patient can withdraw at any time without penalty. We will have a Portuguese and an English version of informed consent and questionnaires.
Potential clarification of different types of pain more specific to a specific location making diagnosis easier and less time consuming. Evolving the patients in research giving them a written report of results after conclusion will be done.

FINANCIAL ASPECTS

No specific sponsor for any part of the protocol is predicted.

ADMINISTRATIVE ASPECTS AND PUBLICATION

.4 Amendments

All substantial amendments will be notified to the responsible ethic committee and to the competent authority. Non-substantial amendments, such as typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons (not the principal investigator) in the submitted study documentation, will not be notified to the responsible ethic committee and the competent authority, but will be recorded and filed by the project leader.

.5 Annual progress report

The project leader will submit a summary of the progress of the study to Hospital da Luz Learning Health every 6 months after initiation. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the study, serious adverse events/serious adverse reactions, other problems, and amendments.

.6 End of study report

The project leader will notify the responsible ethic committee and Hospital da Luz Learning Health of the end of the study within a period of 8 weeks. The end of the study is defined as the last subject's last follow-up visit. In case the study is ended prematurely, the project leader will notify the responsible ethic committee and Hospital da Luz Learning Health, including the reasons for the premature termination. Within one year after the end of the study, the project leader will submit a final study report with the results of the study, including any publications/abstracts of the study, to Hospital da Luz Learning Health.

.7 Public disclosure and publication policy

The responsibility to publish the results of the study is from the main researcher. Study findings will be reported in national and international peer-reviewed journals, regardless of the outcome. Results of the study will also be presented at national and international meetings and conferences. We expect to publish at least 2 papers in the next three to four years. The authors of the publications will include people of the investigator team who were involved in executing and designing the study, but in addition may include other persons having made relevant contributions to the study (e.g. lab technicians, trainees), as decided by the project leader/ principal investigator. The order of authors will be determined after careful consideration of the nature and extent of each person's contribution.

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