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Original article

Endometriosis Index: A software-derived score to predict the presence and severity of the disease

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ABSTRACT

Objective: *To develop a clinical index that will positively predict the presence of endometriosis.*
Design: *Prospective single-center observational study. Setting: A hospital-based institute.*
Patients: *120 patients affected by chronic pelvic pain, infertility or with clinical suspicion of endometriosis. Interventions: Electronic processing of clinical data with software-assistance at the end of each consultation and digital video recording of surgeries.*
Main Outcome Measures: *Endometriosis Index (EI), the score calculated using clinical parameters correlated with macroscopic/microscopic presence or absence of endometriosis.*
Results: *Endometriosis was staged and treated in 95 cases, the remaining 25 women presented benign pathology with no endometriosis. Patients with positive operative findings of endometriosis had a mean (± standard deviation) pre-operative EI score of 22 ± 12, while mean EI value of patients with no operative findings of endometriosis was 8 ± 6 ($p<0.001$). Cumulative distribution of EI shows increasing values from controls to peritoneal, ovarian and deeply infiltrating endometriosis (DIE) (p for trend <0.001). A logistic model showed an OR = 24.7 (95%CI=8.3 to 73.7) of having DIE for women with EI score > 28 (75th percentile value) versus women with EI score ≤ 28; with EI score > 28 this non-invasive test was predictive of DIE with a sensitivity of 72.4% and a specificity of 90.1%.*
Conclusions: *These data suggest that a dedicated Endometriosis Index is effective in identifying patients who would benefit from early surgical management. We propose the use of this non-invasive tool to reduce the delay between the onset of symptoms and a surgical diagnosis of endometriosis.*

KEY WORDS: *Endometriosis, Index, Software, Diagnosis*

Accepted

INTRODUCTION

Endometriosis has significant medical and social impact world-wide. The overall delay between onset of symptoms and actual diagnosis has been calculated as 9.28 years (1). Pooled data from a 9-year single-center study have estimated the prevalence of endometriosis between 8 and 10% (2). At an individual level, chronic pelvic pain leads to years of disability and suffering, with loss of employment, marital discord, divorce and numerous untoward and unsuccessful medical misadventures (3). Clearly, pelvic pain is an important issue in the health care of women contributing to 10% of all outpatient gynecological visits, is responsible for approximately 40% of laparoscopies, and is the indi-

cation for 10% - 15% of hysterectomies (4). The existence of a relationship between chronic pelvic pain symptoms and endometriosis is widely accepted, but various painful pelvic symptoms are normally present in the general population (5). The complex nature of chronic pain and our naïve understanding of its origin, particularly in the setting of endometriosis, results in the use of therapies that generally provide only temporary relief of symptoms (6). The American College and the Royal College of Obstetricians and Gynaecologists have both recently recommend the empirical use of medical therapy before confirming a definitive diagnosis when the risks and benefits of empiric surgery are considered (7). However, endometriosis may be progressive and early laparoscopic diagnosis in patients suffering from this potentially serious disease could be appropriate. Recognizing the known effect and effectiveness of surgical excision on endometriosis (8), the dilemma for individual clinicians is to choose when to operate. Despite several classification systems and questionnaires developed thus far, no standard reference exists for patients suffering from this disabling condition. We propose a tool to determine, at the time of the first consultation, whether a woman would benefit from early surgery to treat her condition versus simply empirical treatment. To address this issue we have created a non-invasive diagnostic Endometriosis Index (EI) from 38 variables and parameters derived by the patient pain evaluation, physician consultation, and diagnostic evidence.

We propose creating a standardized index, taking into consideration evidence-based signs, symptoms and diagnostic criteria (9-13), to preoperatively determine the patients' probability of having endometriosis and determining which patients will gain the greatest benefit from early surgery.

MATERIALS AND METHODS

Population

120 patients, referred to our unit for suspicion of endometriosis, chronic pelvic pain and infertility, were randomly and prospectively evaluated with software-assistance before and after surgery. All women were operated and videos were recorded via hospital intranet. At the time of surgery endometriosis was staged according to the Revised American Society for Reproductive Medicine classification (14) and each case was confirmed by histology. On the base of the information received from surgeons and pathologists endometriosis was sub- classified in peritoneal forms (endometriotic extension < 1 mm underneath the peritoneum), ovarian endometriomata (intra-ovarian endometriotic lesions) and deeply infiltrating endometriosis (DIE) (endometriotic extension > 5 mm underneath the peritoneum) (15, 16). The study was reviewed and approved by the local Institutional Review Board.

Model description

The unified evaluation model is a software real-time calculation based on homothetic transformation (17) of 38 variables and parameters expressed with a normalized score. The exhaustiveness of the symptoms studied was ensured by basing the list on a comprehensive literature review (1, 3-13, 15, 18-23) and on our clinical practice. Endometriosis health profile questionnaires, health-related quality of life instruments and pain evaluation systems previously used in clinical studies (3, 8-10, 13, 18, 24-32) have been carefully evaluated and constitute the educational base of this software assisted health profile assessment.

The final score of EI is generated to be the quantification of the pathological status at the time of each consultation. The variables and parameters were distributed over three components: i) health profile assessment of the patient, ii) medical consultation and iii) diagnostic evidences. This design is adherent with the model structure and the foreseen questionnaire can be filled out on paper or entered directly on the computer. Each component has a collection of values (indicators) grouped according to a logical cascade of questions in the following sections:

i-a) Pain assessment is the result of the following sub-items: *1 Dysmenorrhea* (IDM) + 2 *Non menstrual pelvic pai*n (IDP) + *3 Dyspareunia* (DRS); Characterization of the sensory dimension of pain (CDD) is the result of the following sub-items: *4 Throbbing + 5 Stabbing + 6 Cramping + 7 Hot-burning + 8 Heavy + 9 Tender.*

i-b) Quality of life limitation (LDD) is the result of the following sub-items: *10 Work/School days of absence + 11 Daily activity restriction* and *12 Sleep impairment*).

i-c) Induced dysfunction and physical alteration (SPA) is the result of the following sub-items: gastrointestinal symptoms (*13 Alternating constipation and diarrhea + 14 Rectal tenesmus + 15 Constipation + 16 Diarrhea + 17 Rectal pain*), urinary symptoms (*18 Urinary pain – 19*

Bladder tenesmus – 20 Frequent urination – 21 Dysuria) and headache (*22 Headache – 23 Migraine – 24 Cluster headache*).

ii + iii) Pelvic examination (VM) is the result of the following sub-items: *(25 Grade of fixed uterus + 26 Presence of adnexal cyst(s) + 27 Grade of Douglas tenderness + 28 Presence of infiltrating nodule(s) + 29 Grade of pain at digital exploration)*; Diagnostic evidences (IS) result of the following sub-items: *(30 CA-125 blood assay + 31 Ultrasound finding(s) + 32 CA 19.9 blood assay + 33 Magnetic resonance finding(s) + 34 X-Ray / Computerized Tomography finding(s) + 35 Colonoscopy finding(s))*.

Each record profile is compiled through a sequential data-entry of four panels and the algorithm calculates EI and plots a nomogram on real-time. All indicators are expressed as visual analogue scales (VAS), the left and the right extremes represent respectively the lowest and the maximum value; each variable or parameter contributes to the final EI score on the basis of its weight that it has been assigned to reduce or emphasize its relevance. In the first phase of use, the physicians can over-ride the default setting of the software on the basis of their clinical experience. The operator has the possibility to easily adjust the indicator's weighting.

An inherent model feature, the algorithm calculates meaningful EI values, even in the case of missing or incomplete information. In fact, in real practice, it is unlikely to cover all the data-entry panels when interviewing patients. Beside logistic reasons or practical limitations for having incomplete information, the model also accommodates these critical events and allows for data validation. For instance, it is not possible to consider the indicator score for sexual intercourse pain when, say, a young patient had not (a case where it would not make sense to consider a zero score for this type of pain, because there were no sexual intercourses). The algorithm considers the relative weighting of an indicator (either variable or parameter) by discriminating between zero and *nil* values, so distinguishing a zero scalar number from the absence of indicator (when not applicable or not meaningful). In this latter case, the redistribution of the algebraic, cumulative sum of indicators will only take into account the meaningful values and the EI will be calculated accordingly.

The information hierarchy is therefore treated by the model so that the EI values can still be calculated even when entire sections are not entered. EI software considers several approximation possibilities and allows the physician to decide whether to exclude or emphasize specific information. For example each symptom reported in the field i-c makes the EI higher when correlated to the menses; each of these parameters, in fact, is classified as catamenial by clicking on the check-box named "*synchronous with cycle*". Several patients can be followed over time so that an auto-correlation and a trends analysis give an epidemiological prospect. The software provides a storage template of the heuristic weighted knowledge for further uses.

Statistical Analysis

Categorical data were summarized as number (percentage) of subjects while continuous data as mean ± standard deviation (SD) or as median (minimum – maximum). Univariate associations between endometriosis status and all other variables considered were assessed using chi-square or Fisher exact test analyses for categorical variables and the Kruskall-Wallis, Wilcoxon and Mann Whitney tests (in case of non-normal distributions) for continuous variables. Box plots were used to study distributions of EI score and ASRM score in controls women and in women with different types of endometriosis. A non parametric test for trend across ordered groups was used. Pearson correlation coefficient was used to assess correlation between continuous variables.

A logistic regression model was used to estimate the association between DIE disease and EI score percentiles, adjusting for age of women; the likelihood ratio test was used to assess the statistical significance. Two-tailed probabilities were reported and the p-value of 0.05 was used to define nominal statistical significance. The positive predictive value (PPV) is the percent of women who were predicted to have DIE and who were found to have the disease at surgery. Conversely, negative predictive value (NPV) is the percent of women predicted not to have DIE and who were found not to have deeply infiltrating endometriosis at surgery. The kappa statistic measures agreement between the presurgical assignment and surgical diagnosis.

All analyses were conducted using Stata (version 10; StataCorp., College Station, TX) software.

RESULTS

Endometriosis was staged and treated in 95 cases (the remaining 25 women presented benign pathology with

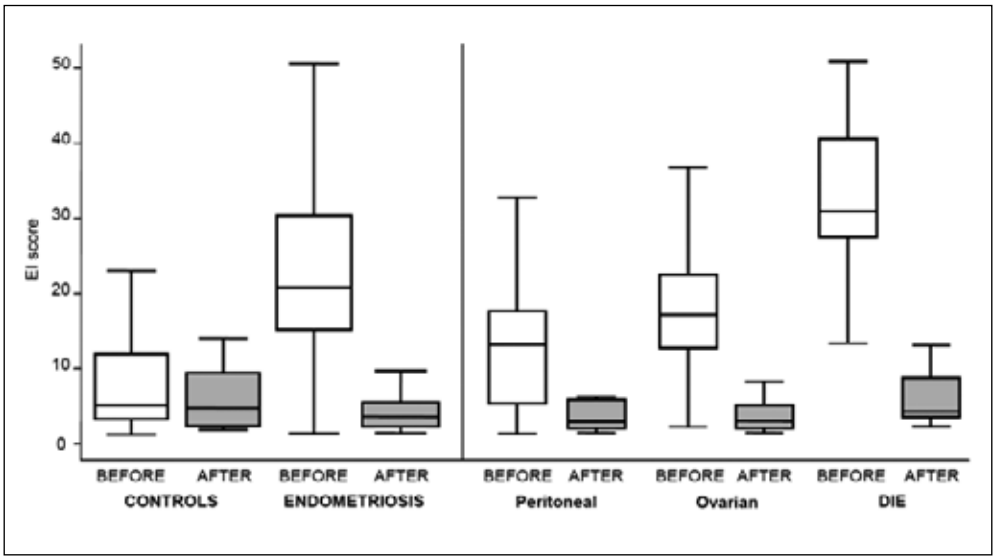

Fig. 1 - *Box plots of EI score before and after surgery in controls and in endometriosis categories.*

TABLE I - CLINICAL CHARACTERISTICS OF THE 120 WOMEN INCLUDED IN THE STUDY

	Diagnosis of Endometriosis (n = 95)	No diagnosis of Endometriosis (n = 25)	P†
Age (years)	36 ± 6	38 ± 7	0.2
Family history of endometriosis	4 (4)	-	-
Current infertility	37 (39)	9 (36)	0.6
Missed school/work (days/month)	4.7 ± 6.5	1.4 ± 3.2	0.001
Sleep impairment (nights/month)	0.7 ± 2.0	0.4 ± 2.0	0.4
VAS for daily activity restriction	3.8 ± 2.6	1.0 ± 1.6	< 0.001
VAS for dysmenorrea	6.5 ± 2.8	3.0 ± 3.0	< 0.001
VAS for non menstrual pelvic pain	2.9 ± 2.9	1.2 ± 2.4	0.001
VAS for dispareunia	3.1 ± 3.1	1.9 ± 2.9	0.07
ASRM score	33.9 ± 29.9	-	-
EI scores before surgery	22.3 ± 11.6	8.1 ± 6.1	< 0.001
EI scores after surgery	3.9 ± 2.5	5.8 ± 4.3	0.2

VAS = visual analogue scale; EI = endometriosis index; ASRM = American Society of Reproductive Medicine endometriosis score; data are expressed as mean ± standard deviation for continuous variables or as number (%) for categorical variables; Mann-Whitney test for continuous variables, chi-square test for categorical variables; † Independent sample t-test was used to test difference in mean age between groups

no endometriosis nor adhesions). Clinical characteristics of patients are shown in Table I.

The software EI calculated before surgery in patients with proven endometriosis resulted in significantly higher values than those of women with no endometriosis (22.3 ± 11.6 vs. 8.1 ± 6.1, p<0.001). The EI scores obtained at the consultations after the excision of endometriosis (25 ± 15 days) become statistically lower than the values recorded in the same patients before surgery (3.9 ± 2.5 vs. 22.3 ± 11.6, p < 0.001) and similar to EI calculated in the group of control (Tab. I) (Fig. 1).

Pre-surgical EI values also showed a modest yet significant correlation to the ASRM scores calculated at the time of surgery (R=0.6, p < 0.001) and the cumulative distribution of EIs shows different and increasing mean values passing from control women to women with peritoneal, ovarian and deeply infiltrating endometriosis (Table II: p for trend < 0.001) (Fig. 1).

A Logistic regression model was used to estimate the risk to have DIE, adjusting for age of women. The analysis showed that women with EI score > 28 (75th percentile) have more than 24 times more risk to have

TABLE II - CLINICAL SCORES VERSUS TYPE OF DIAGNOSIS AT BASELINE

	Controls (n=25)	Peritoneal Endometriosis (n= 14)	Ovarian Endometriosis (n= 52)	DIE (n= 29)	P†
ASRM score	0 ± 0	5.1 ± 9.6	31.8 ± 25.9	51.5 ± 31.5	
	0 (0-0)	3 (0-38)	25 (0-104)	58 (0-112)	< 0.001
EI scores before surgery	8.1 ± 6.1	13.6 ± 9.1	18.6 ± 8.5	33.0 ± 10.1	
	5.1 (1.3-23.1)	13.2 (1.4-32.8)	17.2 (2.3-38.9)	31.0 (13.4-50.8)	< 0.001
VAS for daily activity restriction	1.0 ± 1.6	2.5 ± 2.0	3.3 ± 2.5	5.3 ± 2.3	
	0 (0-5)	2 (0-6)	3 (0-9)	5 (0-9)	< 0.001
VAS for dysmenorrea	3.0 ± 3.0	5.6 ± 3.2	6.0 ± 2.9	7.7 ± 1.8	
	2.0 (0-10)	6 (0-10)	7 (0-10)	8 (3-10)	< 0.001
VAS for non menstrual pelvic pain	1.2 ± 2.4	2.1 ± 2.4	2.4 ± 2.8	4.2 ± 3.0	
	0 (0-10)	1 (0-6)	1 (0-10)	4 (0-10)	< 0.001
VAS for dispareunia	1.9 ± 2.9	2.9 ± 3.1	2.1 ± 2.7	4.8 ± 3.2	
	0 (0-10)	2.5 (0-10)	1 (0-9)	6 (0-10)	0.001

ASRM = American Society of Reproductive Medicine endometriosis score; DIE = Deeply infiltrating endometriosis; † Kruskal Wallis test; data are expressed as mean ± standard deviation, median (min-max). P for trend < 0.001 for each score

TABLE III - SENSITIVITY AND SPECIFICITY OF ENDOMETRIOSIS INDEX (EI)

	deeply infiltrating endometriosis		
EI test	**yes**	**no**	**Total**
EI>28	21	9	30
EI≤28	8	82	90
Total	29	91	120

EI score = 75 corresponds to the 75th percentile of the EI score distribution; Sensitivity=72.4%; Specificity=90.1%: Positive predictive value=70%; Negative predictive value=91.1%; Accuracy (% correctly classified)=85.8%; kappa statistic=0.618

DIE compared to women with EI score ≤ 28 (OR = 24.7, 95%CI = 8.3 to 73.7, p< 0.001). With EI score > 28 the software analysis resulted predictive of DIE with a sensitivity of 72.4% and a specificity of 90.1%. The accuracy (% correctly classified) was 85.8% and the kappa statistic resulted 0.618 (Tab. III).

DISCUSSION

Endometriosis cannot always be cured successfully by current medical and surgical interventions, and attempts for early diagnosis have been overwhelmed by "hit-and-miss" treatments (33). In particular, the lack of a non-invasive method of diagnosis has limited the ability of the clinician to choose appropriate treatment or surgery (26). In this study we have tested the clinical applications of a software-derived score, the Endometriosis Index, created to identify women affected by the disease.

The first step of the project has been the realization of an electronic aid able to save and elaborate the data derived by women at risk of bearing endometriosis; the fields requested by the software to be filled have been specifically designed for a multidisciplinary management of this disease (i.e. gynecologists, anesthetists, general surgeons, urologists, radiologists, pathologists etc.) and contain clinical information derived by the patient, the doctors and the diagnostic evidences (http://www.galliera.it/endometriosi/promoie.html). The first three panels collect data regarding symptoms and the level of patient disability. Dysmenorrhea, non-cyclic pelvic pain and dyspareunia are three distinct bars as VAS; words used to describe pain were brought together, categorized and scaled on a common intensity dimension, in accord to the McGill pain questionnaire (24, 34). Quality of life was determined by assessing the loss of productivity (days of work or study lost in the last month), the inability to perform daily life activities and sleep impairment (nights lost in the last month). The gastrointestinal dysfunctions, urinary symptoms and headache were accurately listed and scaled in accord with recent literature (10, 11, 19, 27, 35). The last panel contains and quantifies the positivity of the pelvic examination maneuvers and

diagnostic tests demonstrated to reveal the presence of endometriosis (3, 4, 7, 13, 21, 26, 36, 37).

At this point the challenge has been to find a way to convert all these clinical data into a number correlated to the presence and severity of endometriosis at the time of the consultation. In order to achieve this goal the clinical variables, their relative level of importance and the algorithm for the software were chosen after an exhaustive literature review and our previous practice (9-13, 17). In the final phase of the project we have validated this novel technology by testing in different situations: pre-surgical presence of endometriosis, absence of disease and post-excision endometriosis-free status.

The results of the present work show that women with endometriotic lesions had pre-operatively EI values higher than those calculated in patients with other benign pathologies (Tab. I – Fig. 1). The significant EI drops observed at consultation after the excision of endometriosis further exemplifies the capability of this non-invasive tool to reveal the presence/absence of disease. To our knowledge this is the first report of a dedicated software able to confirm the effect -- and effectiveness -- of surgical excision on endometriosis (8) in patients managed for pain or impaired quality of life.

In addition, it is worth noting that pre-surgical EI values of patients affected by endometriosis correlate with the ASRM scores calculated at laparoscopy and their averages differ in the three forms of the disease. We consider significant that the EI scores subgroup women affected by endometriosis in patients with peritoneal, ovarian and deeply infiltrating lesions (Tab. II). The evidence that EI levels rise from 'mild' to 'severe' forms of endometriosis emphasizes the sensitivity of the algorithm-regulated software and confirms the difficulty of predicting peritoneal instead of ovarian or DIE (26). At present, superficial endometriosis is considered a normal phenomenon in women at the childbearing age, whereas deep infiltrative endometriosis and endometrial ovarian cysts are the complex and painful manifestations of the condition (38). In accord to these latter evidences we must point out that high EI scores are strongly predictive of aggressive forms of endometriosis even though initial or mild types of disease may be not diagnosed with certainty before surgery. The parameters/variables constitutive of the software, in fact, seem to better unmask the invasiveness of endometriosis rather than the disease itself. Gastrointestinal and genito-urinal symptoms temporally related to the menstrual cycle are suggestive of retroperitoneal foci of disease and are more heavily weighted in the algorithm. These data could explain why the multivariate model showed that an EI score > 28 (75th percentile) is strongly associated (24-fold increased risk - sensitivity of 72.4% - specificity of 90.1%) to the presence of DIE compared to a lower EI score.

The presented data indicate the actual potential of a software-assisted clinical management of patients suspected to bear endometriosis. The first scenario is represented by patients with low EI scores in whom the empirical use of medical therapy could be justified before further consultations. On the contrary, women with alerting / non-diagnostic EI values should be carefully counseled for surgery considering both complications and clinical variables as age, course of infertility, quality of life etc. It is novel that an electronic tool could allow the selection of patients with a high score value to become candidates for a specific presurgical diagnostic work-up to confirm the presence of DIE. A correct preoperative diagnosis is of paramount importance in order to plan an adequate surgical procedure, and minimizes the risks of overlooking endometriotic intestinal or urinary lesions at surgery or of performing an incomplete surgical resection (15). This may eventually help to minimize the postoperative persistence or recurrence of both the lesions and the pain symptoms.

Although the number of patients can be considered still too low to allow definitive conclusions, the pioneering use of the EI score as a screening tool to detect endometriosis proved clinically very effective and offered our patients the possibility to receive an early management of the disease, specific consents, and a dedicated surgical team.

The authors feel that this EI can serve as a non-invasive diagnostic tool, but, can also be useful in the endometriosis community as a standardized communication method. A large multi-centered randomized trial is required to validate this index.

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