RESEARCH ARTICLE

Case–control study to develop and validate a questionnaire for the secondary prevention of endometriosis

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Abstract

Background

Endometriosis is a debilitating gynecologic disease characterized by the implantation of endometrial tissue in ectopic locations, with signs of severe and chronic inflammation. The new knowledge on endometriosis has highlighted the value of secondary prevention through the early diagnosis and treatment of lesions to reduce serious consequences, first of all, infertility and chronic pelvic pain. The purpose of this study is to assess the reliability and validity of the questionnaire, as a tool to precociously identify women with endometriosis, to prevent the progression of symptoms.

Method

We reviewed the literature and selected risk factors, symptoms, and phenotypic traits of the women affected by endometriosis to create the questionnaire divided into 8 modules, with 47 questions. A total of 151 women completed the questionnaires: 51 patients who have endometriosis (the cases) and 100 matched women without endometriosis (the controls). After data collection, bivariate and multivariate analyses were conducted.

Results

We retained four of the significant variables from a step-down logistic regression, namely chronic pelvic pain, dyspareunia with VAS ≥3, painful defecation, and acne, to develop a final “predictive” logistic model achieving 90.2% sensitivity and 75% specificity.

Conclusion

Our pilot study demonstrated that the questionnaire provides a powerful tool for the secondary prevention of endometriosis.
Introduction

Endometriosis is an estrogen-dependent, chronic gynecological disease characterized by the presence of endometrial glands and stroma outside the uterus, which can result in a broad spectrum of symptoms, including dysmenorrhea, pelvic pain and infertility [1]. The etiopathogenesis of endometriosis is uncertain but is probably a multifactorial process resulting in a heterogeneous disease [2,3]. Women affected by this pathology have suffered for years from chronic pelvic pain, as well as from pain during the menstrual cycle and sexual intercourse [4,5]. Recent studies revealed that the disease is present in around 1.5% of the general female population and 6–15% of hospitalized women [4]. The data provided by the Italian Agency for Medicinal Products report that in Italy the prevalence of endometriosis in asymptomatic women varies from 2% to 22%, depending on the diagnostic criteria used and the population studied: in women with severe dysmenorrhea and chronic pelvic pain the percentage ranges from 40 to 60% and in women with subfertility it sets around 20% and 30% [6].

Currently, hormonal and biological therapies for the treatment of endometriosis are under intense clinical investigation [7]. However, the majority of these compounds have only been evaluated in pre-clinical studies or early clinical trials. Thus, further extensive clinical research is necessary. Of note, late clinical trials on gonadotropin-releasing hormone antagonists (GnRH-ant) showed the most promising results for the treatment of endometriosis [7].

Although ultrasound evaluation has become the primary test in the diagnosis of pelvic endometriosis [8], the diagnosis of endometriosis can be confirmed only upon a direct visualization of the lesions; therefore the gold standard to identify and treat it therapeutically (removal of tissue, vacuolation, and lysis of any adhesion) is laparoscopy [5], which is a costly and invasive technique. Consequently, barring severe abdominopelvic symptomatology, a large part of the population relies on less invasive methods to investigate the disease, such as ultrasounds (US), Magnetic Resonance Imaging (MRI), and specific blood tests (looking for Ca-125 and Ca-19-9 markers). Besides, the disease’s progression can be temporarily kept under control through hormonal pharmacological [9], postponing the surgical operation, especially in young women of reproductive age [10]. In any case, endometriosis is not easy to identify, and the process can take many years: from 8 to 11 years [5]. Reducing the delay in the diagnosis is paramount to prevent the most severe consequences of endometriosis, first of all, infertility and chronic pelvic pain [4,5,11]. The purpose of this study is to validate a simple and effective questionnaire to precociously identify women with endometriosis, leading them to the correct diagnostic approach and the most appropriate treatment.

Experimental section

Study design and patients selection

The investigation has been carried out in two stages: one focused on the development of an instrument for secondary endometriosis prevention and the other on its validation. During the first stage, we reviewed the literature and selected risk factors, symptoms and phenotypic traits of the women who have endometriosis to create a questionnaire. A combination of six literature databases was searched (PubMed, MEDLINE, Google Scholar; Web of Science, Scopus, Embase) to retrieve all relevant references. Subsequently, we asked 20 women, patients at the Reproductive Medicine Unit (RMU) of the Institute for Maternal and Child Health—IRCCS “Burlo Garofolo” in Trieste (Italy), to test its actual intelligibility, and we modified it according to the results. The second stage of the investigation was carried out through a case-control study. Patients with endometriosis had contacted the RMU because of their fertility problems, and they received, through the laparoscopy, a diagnosis, which, in most of the cases,
has been confirmed by a histological report. The controls were enrolled from the list of healthy, asymptomatic women in the 1 trimester of pregnancy, who had contacted the IRCCS “Burlo Garofolo” to undergo the first-trimester obstetric ultrasound scan. Controls were women with spontaneous conception and did not include women who had been diagnosed with endometriosis or with any other symptomatic gynecological disease. The ultrasound, performed for unrelated reasons, confirmed they did not present lesions due to endometriosis.

Furthermore, considering a negative case history, we were reasonably able to exclude endometriosis or other gynecological diseases. We also excluded from the study women affected by active chronic inflammatory bowel disease, since the disease could confuse the gastrointestinal symptoms, as well as foreign women who were not fluent in Italian. The women enlisted were of reproductive age, and an effort was made to create a group as homogeneous in age as possible to the enrolled cases. After signing a written informed consent form, women (both cases and controls) were interviewed in-person to answer the questionnaire. The study did not include minors, and was approved by the Institutional Review Board of the Institute for Maternal and Child Health–IRCCS Burlo Garofolo, Trieste (06.12.18).

**Questionnaire design**

The questionnaire (S1 File) is divided into 8 modules, with 47 questions in total. The first module focuses on the responder’s knowledge of the disease. The issues of the other 7 modules concern physiological case history, family history, remote medical history, phenotypic traits, gastrointestinal symptoms, urinary symptoms, and, lastly, gynecological history.

**Physiological case history.** Physiological case history includes age, weight, height, Rhesus factor (Rh), and nutritional habits. Literature reveals that endometriosis is a disease affecting women of reproductive age [11,12], whose Body Mass Index (BMI) is lower than the one of controls [13,14]. In particular, it has been reported that for every unit increase in BMI (kg/m²), there was an approximate 12–14% decrease in the likelihood of being diagnosed with endometriosis. Moreover, multivariate analysis showed that Rh-negative women are twice as likely to develop endometriosis [15]. Finally, it seems that eating fruit and vegetables may have a protective effect against the disease, unlike red meat and cured meat [12].

**Family history.** Regarding family history, the questionnaire investigates whether the women interviewed had mothers or sisters affected by endometriosis, considering the familiarity a major risk factor [5,16].

**Remote medical history.** The remote medical history investigates, as reported in the literature, the relation between endometriosis and the following pathologies: allergies and asthma [17–20], systemic lupus erythematosus, rheumatoid arthritis, Sjögren’s syndrome, multiple sclerosis, coeliac disease, autoimmune thyroiditis [21–25], acne [26–28] and migraine [29,30].

**Phenotypic traits.** In the module on phenotypic traits, the questions focused on natural hair’s color, eye’s color, complexion, skin sensitivity to sun exposure, number of nevi, and freckles. Some studies report a connection between endometriosis and red hair—although other studies contradict this association [31–33]—and between endometriosis and blue eyes [34]. It also appears that women affected by endometriosis have fairer skin, more nevi, and freckles and are more sensitive to sunlight [35,37].

**Gastrointestinal symptoms.** The section concerning gastrointestinal symptoms investigated non-menstrual abdominal pain, constipation, meteorism, flatulence, defecatory urgency, and feeling of incomplete defecation. This assessment was based on the Visual Analogue Scale for Irritable Bowel Syndrome (VAS-IBS), a validated questionnaire that aims to investigate gastrointestinal symptoms in patients not affected by organic diseases [38].
Urinary symptoms. Regarding urinary symptoms, the questions were focused on incomplete bladder emptying, pollakiuria, urinary urgency, nycturia, and dysuria without bacterial cystitis. We have paid particular attention to the differences between urination with and without the menstrual cycle. The questions have been taken from the American Urologic Association Symptom Index (AUASI), as modified by an Italian study group [39].

Obstetric-gynecological history. The obstetric-gynecological history investigated: any use of hormonal contraceptives, the reason why they are taken, any previous abortion, pregnancy, the age at which the menstrual cycle began, its regularity, frequency, the heaviness and length of menstrual bleeding, dysmenorrhea, any consequence on usual daily life, painful defecation during menstrual cycle, dyspareunia and chronic pelvic pain unrelated to the menstrual cycle [40]. Some studies showed that women who have endometriosis are more likely to have experienced premature menarche and more regular and shorter menstrual cycles, with more massive and longer bleeding than controls [41]. On the other hand, it appears that parity is inversely connected to the risk of endometriosis [5,12]. We investigated the degree of dysmenorrhea asking if the pain was so intense that it required the use of drugs and if it made usual daily activities impossible, when not treated [41–44]. For dyspareunia, the study used a Visual Analogue Scale (VAS) [45]. Painful defecation during the menstrual cycle and chronic pelvic pain seem to be very related symptoms to deep endometriosis [45].

Statistical analysis

Once the information had collected, the data entry was conducted with EpiData 3.1 (The EpiData Association, Odense M, Denmark), statistical analyses were carried out with the Stata/IC 14.1 software (StataCorp LP, College Station, U.S.A.) and R 3.1.3. (The R Foundation for Statistical Computing, Vienna, Austria). Bivariate analyses were conducted using the two-tailed Fisher’s exact test for tables with categorical variables, the nonparametric Mann-Whitney test, which compares the values of continuous variables in two different groups, and logistic regressions with a single independent variable. Bivariate and multivariate logistic regressions were implemented through a specific method called Firth’s penalized likelihood approach. This procedure makes it possible to manage small samples and, in particular, to manage cases that would present zero frequencies in the frequency tables, which would not allow the use of conventional approaches. We included variables that were significant in the bivariate analysis, while a step-down procedure discarded all the variables not significantly associated with the outcome, starting with those with a higher p-value. After obtaining a model with only significant variables, all the previously discarded variables were re-entered one-by-one to ascertain their significance. We thus obtained a final “predictive” logistic model. We also tried to generate a model adopting a decision tree method—a CART model using the R software—but the result was not as satisfactory as the one obtained with multivariate logistic regression.

Results and discussion

Amongst the various questionnaires reported in the literature that investigated different aspects of endometriosis, none had secondary prevention as their primary objective [39,46–48]. For instance, a questionnaire to measure painful symptoms of endometriosis in a comprehensive and multidimensional way, including the patient’s perspective, has been recently reported, and it holds promises for improving the management of endometriosis [47]. Indeed, besides diagnostic purposes, measuring and monitoring the painful symptoms of endometriosis would be fundamental in providing more accurate clinical decisions, and significantly facilitate follow-up of therapy. In another study, a questionnaire evaluated a selected population of women undergoing surgery for chronic pelvic pain with suspected bladder...
endometriosis [39]. Also, a disease-specific questionnaire to measure the long-term impact of endometriosis on different aspects of women’s lives has been proposed to provide a better understanding of the effects of endometriosis and to meet the needs of women better [48]. Nnoaham et al. reported a complex symptom-based model to predict the endometriosis stage among symptomatic women, to prioritize women for surgical investigation and reduce time to diagnosis before undergoing their first laparoscopy [46].

This is the first study that proposes the use of a questionnaire for the secondary prevention of endometriosis.

Characteristics of the study population

We enrolled 151 women: 51 patients who have endometriosis and 100 healthy controls. All the patients enrolled in the study were Caucasian Italian adults with an average age of 35 years. Demographic characteristics are reported in Table 1.

Analysis of the relationship between variables and endometriosis

In its first stage, the questionnaire focused on the knowledge of endometriosis. An American study [49] carried out on women and men revealed that there is a good knowledge of endometriosis among women affected by this disease, but a very limited or no one at all among healthy individuals or those who do not know any affected woman. Our study shows that all affected women were informed about their pathology, with more than 70% of them having complete and in-depth knowledge of it. Unexpectedly, more than 70% of non-affected women were also aware of the problem, even though only 10% had complete knowledge of it. Besides, more than 70% of women, both in the cases and controls stated that they were aware that endometriosis could affect adolescent girls. Social class and education of the women interviewed might be important confounders, but this good result could be explained by the effort made by the Region Friuli Venezia Giulia to tackle the problem, financing several information and awareness campaigns.

The second part of the questionnaire focused on symptomatology. The association between endometriosis and some risk factors was controversial in the literature, which, in the beginning, made the development of the questionnaire challenging. The strength of our research lies in the fact that the women in the control group underwent pelvic ultrasound, and we are thus reasonably sure they were free from a gynecological condition. Furthermore, the questionnaires were handed out to the women in direct contact, making sure they fully understood each question, thus guaranteeing precise and accurate answers. The results of the bivariate analysis (firth logistic regression analysis), carried out to study the association between the outcome and each variable considered in the second part of the questionnaire, are shown in Table 2 (significant associations) and Table 3 (not significant associations). A recent Swedish study aimed to assess the gastrointestinal symptoms connected with endometriosis using the Visual Analogue Scale for Irritable Bowel (VAS-IBS) [38]. Our research assesses the gastrointestinal symptoms adopting a similar approach, and its results are in line with the most important scientific studies. It highlighted how: 1) cases suffer from non-menstrual abdominal pain for more than 2–3 days per month more often than controls (67% vs. 16%); 2) cases who reported to suffer “constantly” from constipation are more than controls (30% vs. 0%); 3) cases who suffer from meteorism for more than 1 day per week are more than controls; 4) defecatory urgency and incomplete defecation are more common in women affected by endometriosis. However, we need to pay attention to the assessment of this kind of patients, because the irritable bowel syndrome is a pathology that presents a wide range of symptoms in common with the endometriosis such as lumbago, lethargy, fatigability, urological and gynecological
Table 1. Demographic characteristics.

|                          | Cases (n = 51) | Controls (n = 100) | p*      |
|--------------------------|---------------|--------------------|---------|
| Age (years)              | 36.9 (4.5)    | 34.2 (4.7)         | 0.0006  |
| Weight (kg)              | 62.8 (10.6)   | 60.2 (7.8)         | 0.10    |
| Height (m)               | 1.67 (0.6)    | 1.65 (0.1)         | 0.15    |
| BMI**                    | 22.5 (3.4)    | 22.1 (2.8)         | 0.36    |
| Rh+ frequency %          | 39/49 (80)    | 80/94 (85)         | 0.48    |
| Contraceptive use frequency % | 8/49 (16)    | 24/94 (26)         | 0.29    |
| Even had spontaneous abortions | 36/51 (71) | 64/90 (71) | 1.000   |

*p-values from Mann-Whitney rank-sum test.

BMI = Body Mass Index.

**p-values from two-tailed Fisher exact test.

https://doi.org/10.1371/journal.pone.0230828.t001

Table 2. Variables significantly associated with endometriosis (bivariate analysis).

| Variables                                 | Cases (n = 51) | Controls (n = 100) | OR     | 95% CI   | P     |
|-------------------------------------------|---------------|--------------------|--------|----------|-------|
| Age                                       | 36.9 ± 4.4    | 34.2 ± 4.7         |        |          | 0.006 |
| Allergies                                 |               |                    |        |          |       |
| Food                                      | 5(10%)        | 0(0%)              | 23.8   | 1.3–439  | 0.033 |
| Drugs                                     | 9(18%)        | 4(4%)              | 4.8    | 1.5–15.6 | 0.009 |
| Acne                                      | 15(29%)       | 14(14%)            | 2.5    | 1.1–5.7  | 0.025 |
| Hair color; red—blond                     | 1(2%)         | 19(19%)            | 0.12   | 0.02–0.68 | 0.016 |
| Abdominal pain > 2–3 day/month            | 34(67%)       | 16(16%)            | 10.1   | 4.8–23.1 | 0.000 |
| Chronic constipation                       | 15(29%)       | 0(0%)              | 85.4   | 5.0–1463.2 | 0.002 |
| Meteorism > 1 day/week                    | 18(35%)       | 14(14%)            | 3.3    | 1.5–7.3  | 0.003 |
| Urgency in defecation                     | 6(12%)        | 0(0%)              | 28.7   | 1.6–520.7 | 0.0023 |
| Incomplete defecation                     | 25(49%)       | 26(26%)            | 2.7    | 1.3–5.6  | 0.005 |
| Urgency in urination > 1 time on 5       | 14(27%)       | 7(7%)              | 4.8    | 1.8–12.6 | 0.001 |
| Dysuria > 1 time on 5                     |               |                    |        |          |       |
| During urination                          | 11(22%)       | 3(3%)              | 7.9    | 2.3–27.6 | 0.001 |
| At the end of urination                   | 9(18%)        | 2(2%)              | 8.8    | 2.1–37.1 | 0.003 |
| Painful urination during menstruation     | 15(29%)       | 1(1%)              | 41.25  | 5.2–323.6 | 0.000 |
| Taking the pill for dysmenorrhea          | 19(44%)       | 4(6%)              | 17.8   | 5.3–59.8 | 0.000 |
| Successful pregnancies                    | 15(29%)       | 49(49%)            | 0.43   | 0.21–0.88 | 0.023 |
| Heavy menstrual flow                      | 27(53%)       | 24(24%)            | 3.8    | 1.8–8.0  | 0.000 |
| Short cycle length                        | 28(55%)       | 28(28%)            | 3.4    | 1.6–7.2  | 0.001 |
| Cramps during the menstrual cycle which require the assumption of drugs | 43(68%) | 20(20%) | 21.5 | 8.7–52.9 | 0.000 |
| Dyspareunia (VAS ≥ 3)                     | 36(71%)       | 10(10%)            | 20.3   | 8.5–48.6 | 0.000 |
| Occasional (less than once every four intercourses) | 13(25%) | 17(17%) | 4.5 | 1.8–11.3 | 0.001 |
| Recurrent (about half the time)           | 14(27%)       | 4(4%)              | 19.0   | 5.7–63.3 | 0.000 |
| Always                                   | 11(22%)       | 0(0%)              | 135.4  | 7.5–2436  | 0.001 |
| Painful defecation                        | 26(51%)       | 2(2%)              | 51.0   | 11.3–229.3 | 0.000 |
| Pelvic pain that lasts longer than six months | 18(35%) | 0(0%) | 111.0 | 6.5–1892.5 | 0.0001 |

https://doi.org/10.1371/journal.pone.0230828.t002
problems. The overlapping symptoms of the irritable bowel and endometriosis cause many problems for the diagnosis, and it is often not possible to identify where one pathology ends, and the other begins. Recent studies theorized a possible coexistence of the two diseases since the gastrointestinal symptoms of endometriosis are as common as gynecological ones, but only 8% of patients show intestinal lesions that can be identified with laparoscopy [50].

In the clinic assessment of the women affected by endometriosis, it is also important to establish whether the urinary tracts are involved [51,52]. This pathology is likely to worsen the pelvic pain and urinary symptoms of the women affected by endometriosis or cause the urinary symptomatology itself. Previous studies [45,53] showed that affected women find defecation and urination more painful during menstruation, which our study confirmed, especially in connection with deep endometriosis. Recently, an Italian group created a questionnaire to diagnose bladder endometriosis before surgery, starting from the American Urologic Association Symptom Index (AUASI) [39]. In our study, we presented the same questions. Compared

### Table 3. Non statistically significant variables associated with endometriosis (bivariate analysis).

| Variables                      | Cases (n = 51) | Controls (n = 100) | P    |
|--------------------------------|---------------|--------------------|------|
| Weight (kg)                    | 62.8 ± 10.6   | 60.2 ± 7.8         | 0.10 |
| Height (m)                     | 1.67 ± 0.6    | 1.65 ± 0.1         | 0.15 |
| Rhesus Factor                  | 10/49 (20%)   | 14/94 (15%)        | 0.48 |
| Portions fruit/vegetables      | 2.3 ± 1.1     | 2.5 ± 1.3          | 0.35 |
| Portions meat/sausages         | 2.5 ± 1.3     | 2.7 ± 1.6          | 0.45 |
| Mother affected                | 3/51 (6%)     | 3/100 (3%)         | 0.40 |
| Sister affected                | 1/26 (4%)     | 2/56 (4%)          | 1.00 |
| Asthma                         | 3/51 (6%)     | 10/100 (10%)       | 0.54 |
| SLE                            | 1/51 (2%)     | 0/100 (0%)         | 0.33 |
| Rheumatoid arthritis           | 0/51 (0%)     | 1/100 (1%)         | 1.00 |
| Coeliac disease                | 2/51 (4%)     | 3/100 (3%)         | 1.00 |
| Autoimmune thyroiditis         | 7/51 (14%)    | 11/100 (11%)       | 0.61 |
| Migraine                       | 24/51 (47%)   | 37/100 (37%)       | 0.29 |
| Eyes color                     |               |                    |      |
| Blue-gray                      | 13/51 (25%)   | 33/100 (33%)       | 0.34 |
| Green-hazelnut                 | 16/51 (31%)   | 22/100 (22%)       | 0.61 |
| Complexion                     |               |                    |      |
| Pale                           | 6/51 (12%)    | 13/100 (13%)       | 0.92 |
| Fair                           | 20/51 (39%)   | 45/100 (45%)       | 0.95 |
| Cutaneous nevus                |               |                    |      |
| A lot                          | 12/51 (24%)   | 11/100 (11%)       | 0.91 |
| Many                           | 16/51 (31%)   | 37/100 (37%)       | 0.55 |
| Freckle                        |               |                    |      |
| Many                           | 5/51 (10%)    | 10/100 (10%)       | 0.85 |
| Sun sensitivity                |               |                    |      |
| High                           | 21/51 (41%)   | 40/100 (40%)       | 0.34 |
| Incomplete emptying bladder > 1–2 times | 3/51 (6%) | 0/100 (0%) | 0.079 |
| Urination within 2 h from previous | 29/51 (57%) | 66/100 (66%) | 0.29 |
| Menarche early                 | Mean age 12.4 (sd 1.5) | Mean age 12.8 (sd 1.6) | 0.075 |
| Miscarriages                   | 15/51 (29%)   | 36/100 (36%)       | 0.47 |
| Spontaneous abortions          | 15/51 (29%)   | 26/100 (26%)       | 0.70 |
| Regular cycle                  | 43/51 (84%)   | 74/100 (74%)       | 0.21 |

https://doi.org/10.1371/journal.pone.0230828.t003
to controls, women with endometriosis reported more often a feeling of not complete emptying of the bladder, more than half of the times when urinating. We also identified an association with the urinary urgency: women reporting difficulty in delaying urination in at least one out of five times are more likely to suffer from bladder endometriosis. Our study revealed a relation between pain during or after urination and endometriosis. Cases reported suffering from dysuria more often than controls in more than one out of five urination events. We specified that the questions concerning urinary symptoms are linked to the absence of infection of the lower urinary tract because any possible bacterial cystitis could have distorted the symptomatology related to endometriosis. It is important to consider that endometriosis seems to be associated with interstitial cystitis, also known as bladder pain syndrome. A recent US study stated that many of the women who report chronic pelvic pain suffer both from endometriosis and interstitial cystitis, although the causal relationship between the two is still unknown [54].

We registered a significant result concerning the reason for taking the contraceptive pill: cases stated that their main reason was menstrual pain, while for controls, it was contraception. Previous research [44] showed that women who started hormonal contraceptive therapy during adolescence due to major primary dysmenorrhea are more likely to be diagnosed with endometriosis as adults, which is why the reason for taking the pill has been deemed important to investigate. In line with the literature [3,12], our study registered parity as a factor inversely associated with the risk of endometriosis.

Several previous studies [2,7] have shown that the characteristics of the menstrual cycle are strictly related to endometriosis: regular, short cycles and heavy bleeding lasting for more than seven days are associated with the development of the disease. This statement is in agreement with the pathogenetic theory of retrograde menstruation. Indeed, the pelvic contamination, as well as the implant risk, is higher due to more regular short periods and heavy bleeding lasting for more than seven days [3,7,45]. In our study, we did not register any connection between regularity of menstrual cycle and endometriosis. We confirmed, however, the association with short menstrual cycles: among cases, several women stated they had menstrual cycles shorter than 28 days, while among controls, several women had cycles exceeding 34 days. In agreement with the literature, our study registered a significant relation between heavy menstrual bleeding and endometriosis, while there is no statistically significant association with the length of the menstrual bleeding. The firm association between endometriosis and dysmenorrhea is now confirmed; dysmenorrhea is a symptom that affects most of the women with endometriosis, and it is often so strong to confine women to bed, becoming the main responsible for the absence from school and work [35–38]. Following previous studies, we also found that women with endometriosis suffer from intense cramps during the menstrual cycle, which requires the assumption of drugs and full rest more often than controls (68% vs. 4%). The severity of dysmenorrhea affects daily life, causing absenteeism at each menstruation in 54% of cases and only 6% of controls. The result is essential because it emphasizes once more the importance of the relation between dysmenorrhea and endometriosis, and the repercussions this pathology has on the patients’ quality of life.

Chapron et al. [45] proved that dyspareunia is a common symptom among women affected by endometriosis and established that severe dyspareunia with VAS ≥ 8 or complete apareunia are reliable predictors of deep posterior endometriosis. Our research confirmed that the association between dyspareunia and endometriosis is statistically significant; in particular, the risk of suffering from endometriosis among women who reported a ≥ 3 score in the VAS scale is increased by 20 times. Schliep et al. [55] have recently conducted a study to assess abdominal and pelvic pain among women who had to undergo a surgical operation, revealing that women with endometriosis had been suffering from more severe chronic pelvic pain and for a longer time than the others. Our investigation reached the same result, confirming that a
A woman with chronic pelvic pain is 111 times more at risk of suffering from endometriosis than a woman without.

Final predictive logistic model to identify endometriosis

Finally, we carried out a Firth Logit multivariate logistic regression analysis (Table 4), adopting a step-down procedure. Only four of the significant variables from the bivariate analyses were retained, by the final multivariate model, as significantly associated with the outcome: chronic pelvic pain, dyspareunia with VAS rating $\geq 3$, painful defecation during the menstrual cycle and acne in the adolescent years. The Area Under the receiver operating characteristic Curve (AUC) reached 0.9154. Using the regression coefficients reported in Table 4, and the following predicted probability formula: 

$$\text{Prob} = \frac{1}{1 + e^{-(2.6987 - 4.350162 - A + 2.731929 - B + 2.619159 - C + 1.356307 - D)}}$$

and setting a cut-off value of $\geq 0.207113$, the resulting model identified endometriosis cases in our sample with 90.2% sensitivity and 75% specificity. This procedure demonstrates that it is possible to identify nine out of 10 women affected by endometriosis, with 25% of false positives. Besides, it is interesting to note that this cut-off represents positivity to any of the four variables, or any combination of these.

Limit and strength

A limitation of our case-control study design lies in the fact that the women in the control group were not evaluated by laparoscopy. However, they underwent pelvic ultrasound by an operator with a high level of expertise in gynecological ultrasonography. Overall, we are reasonably sure they are healthy from a gynecological point of view according to their asymptomatic status and to the family and medical history negative for endometriosis, infertility, and chronic pelvic pain.

One strength of this study is the homogeneity of the study population in terms of both ethnic background and education regarding clinical aspects of endometriosis. Indeed, despite the expectations of performing differently, we found out that women involved in the study were sufficiently aware of the medical context within which they were carrying out their questionnaire and demonstrated adequate knowledge of the operating environment. These results provide evidence of the effects that information campaigns aimed at awareness-raising and knowledge generation may have on their respective target groups. Furthermore, a sole operator distributed the questionnaires and interviewed women in person, making sure they fully understood each question to guarantee precise and accurate answers.

One issue with the current study was that the connection between endometriosis and some risk factors was controversial in the literature, which, in the beginning, made challenging the development of the questionnaire. However, a combination of six literature databases were searched (PubMed, MEDLINE, Google Scholar; Web of Science, Scopus, Embase) to retrieve all relevant references.

The prior research aimed to create complex symptom-based models to predict the endometriosis stage among symptomatic women, to prioritize women for surgical investigation and reduce time to diagnosis before undergoing their first laparoscopy [46]. In contrast, our pilot study aimed at a simple diagnostic test to detect endometriosis in the general population. Therefore in the future, besides more extensive confirmatory studies are required to examine whether findings on its efficacy can be generalized, it will be essential to explore the potential use of this questionnaire as a screening test distributed by health care providers beyond the specialized clinical settings.
Conclusions

This study has analyzed the results of a questionnaire which aimed to identify patients at high risk for endometriosis, through the association with risk factors and symptomatology. Its purpose was to shape up a prediction model that could identify women with suspected endometriosis to lead them to correct diagnostic procedures and rapid diagnosis. The results of our study reveal that women who suffer from food or drug allergies and who suffered from severe acne during adolescence are more at risk of being affected by endometriosis. We also found that women are also at risk when reporting non-menstrual abdominal pain for more than 2–3 days per month when regularly suffering from constipation, meteorism for more than one day per week, with defecatory urgency, incomplete defecation, urinatory urgency in one urination event out of five, dysuria during or at the end of urination more than one every five urination events. The risk of developing endometriosis is very high also for women who have taken the pill to cope with severe menstrual pain, nulliparae, women with a menstrual cycle shorter than 28 days, with heavy bleeding or suffer from chronic pelvic pain. Fall into the same type of category also women who suffer from severe dysmenorrhea which forced them to take drugs, stay home from school or work, who report painful defecation during the menstrual cycle, describe sexual intercourse as very painful more than half of the times—with a score higher than 3 in the VAS scale. In an effort to simplify the questionnaire, we conducted a step-down logistic regression analysis and could select only four of these variables, namely chronic pelvic pain, dyspareunia with VAS $\geq 3$, painful defecation and acne, which are the optimal combination and guarantee the best sensitivity and specificity. With this method, the prediction model achieves 90.2% sensitivity and 75% specificity.

In conclusion, we believe that our questionnaire could provide a powerful tool for the secondary prevention of endometriosis. Moreover, emerging evidence suggests that adolescents are subject to endometriosis much more often than previously thought [11], therefore a screening tool designed to allow young women to identify potential symptoms of endometriosis could facilitate the initial discussions between patients and physicians. The possibility to diagnose endometriosis precociously in young women could spare them years of pain and frustrations and, slow the course of the disease, and it would be possible to increase their reproductive potential.

Supporting information

S1 File. Questionnaire in original language ad English.

(DOCX)

Acknowledgments

We thank Dr. Martina Bradaschia for the English revision of the manuscript.
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