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49 **Abstract**

50

51 **Objective**: To analyze the literature and expose best evidence available regarding the benefit

52 of pelvic examination for women with suspected endometriosis

53 **Methods**: the AGREE II and GRADE systems for grading scientific evidence.

54 **Results**: Endometriosis is characterized by the heterogeneity in its clinical presentation with

55 many different symptoms reported by patients. In the literature, questioning for each

56 symptom has a high sensitivity, reaching 76–98%, but lacks specificity (20 – 58%). The

57 symptom-based approach is limited by its low specificity, the absence of external validation

58 for most of the models developed and the inability to characterize the extent of the disease,

59 which could have major implications in the decision – making process. The latest systematic

60 review and meta-analysis included a total of 30 studies with 4,565 participants, compared

61 the diagnostic performance of several modalities for endometriosis. Physical examination

62 had a pooled sensitivity of 71% and a specificity of 69%, with an average diagnostic accuracy

63 of 0.76. Overall, the value of pelvic examination is conferred by its high positive likehood

64 ratio and specificity. Besides its diagnostic value, pelvic examination improves patients'

65 management by allowing the identification of a possible myofascial syndrome as a

66 differential diagnosis. It also increases the quality of the preoperative workup and influences

67 the quality of surgical excision and decreases the time to diagnosis.

68 **Conclusion**: Despite the lack of studies in the primary care context, pelvic examination

69 (vaginal speculum and digital vaginal examination) increases the diagnostic value for

70 suspected endometriosis in association with questioning for symptoms.

71 **Keywords**: Endometriosis; Pelvic Examination; Symptoms; Diagnostic ;

72

Introduction

73   **Introduction**

74   Recent international guidelines have modified gynecological follow-up in

75   asymptomatic women by limiting the indications for pelvic examination [1]. Systematic

76   follow-up consisted of symptom questioning and pelvic examination including vulvar

77   inspection, speculum vaginal examination, and digital vaginal examination. Studies have

78   reported that these medical examinations can be stressful and are perceived as intrusive

79   with negative experiences [2]. However, when symptomatic, most women will accept pelvic

80   examination if required for diagnosis purpose and if the procedure is performed by a

81   qualified health professional [3].

82   Endometriosis, particularly in its advanced stages, is a well-known cause of disabling

83   pelvic pain and infertility [4]. It is estimated that up to 10% of women of reproductive age

84   and 50% of infertile women have a huge impact on quality of life in some cases [5,6]. In

85   patients with chronic pelvic pain, 11 studies ranged the prevalence of endometriosis with

86   great disparities between 2 and 74% [7]. This disease represents a public health issue with

87   considerable cost at both individual and society levels [8].

88   Endometriosis diagnosis is a matter of concern. As diagnosis is often the gatekeeper to

89   treatment, the faster the diagnosis, the sooner appropriate treatment can be introduced.

90   The latest "state of the art" review by Pascoal et al. perfectly underlines the diagnostic

91   difficulties of this pathology and the imperfect nature of each method, with its strengths and

92   weaknesses, from which the questioning and pelvic examination do not escape [23]. Indeed,

93   women can present with great disparities of non-specific symptoms and some of them are

94   even completely asymptomatic (independently of the extent of anatomic lesions). Pelvic

95   examination is currently part of first line diagnostic strategy in women with suspected

96   endometriosis in both European and French HAS Guidelines [9,10]. Whenever possible,

97 pelvic examination associated with the questioning is the first step of the diagnostic

98 algorithm. Several authors reported a benefit of clinical examination to improve diagnostic

99 strategy [11]. The question of the benefit of pelvic examination in patients with suspected

100 endometriosis is all the more relevant that it usually also aims to identify painful spots that

101 could indicate endometriosis. The French college recently issued guidelines on the benefit of

102 pelvic examination in various situations, in either gynecology or obstetrics [12]. This

103 examination must be carried out with particular caution, especially in the context of

104 endometriosis because of its painful nature in these patients and women should be informed

105 of the modalities and expectations prior consent to be examined.

106 The aim of this work was to analyze the literature and expose best evidence available

107 regarding the benefit of pelvic examination for women with suspected endometriosis

Methods

In collaboration with the methodologist in charge of the aforementioned guidelines, a search strategy was designed using key terms and keywords. The search was limited to human studies written in English or in French. The PubMed platform was used to search MEDLINE. MeSH terms and non-MeSH terms were used. Search equations used "AND" and "OR" on MEDLINE/PubMed. Key words used for this PICO were: "endometriosis"; "deep endometriosis"; "vaginal endometriosis"; "pelvic examination" ; "physical examination" ; "vaginal speculum"; "vaginal examination"; "imaging"; "MRI"; "pelvic ultrasound". Each study was evaluated independently, and an overall level of evidence was processed once the review completed.

In this work, pelvic examinations referred to vulva inspection, speculum examination of the vagina and the cervix and palpation through manual examination of internal genital organs (vagina and cervix, uterus corpus, adnexa) and hypogastric region. The question of rectovaginal examination was not considered in these guidelines due to the limited data available in the literature.

124   **Results**

125   The main studies reporting on the relevance of physical examination for the diagnostic of

126   endometriosis are reported in Table 1.

127   <u>Value of the questioning for symptoms in the diagnostic strategy of patients with suspected</u>

128   <u>endometriosis</u>

129   <u>Elements of the systematic questioning in women with suspected endometriosis</u>

130   Many studies evaluated the relevance of the questioning for symptoms in women

131   with suspected endometriosis. Painful symptoms of deep endometriosis have characteristics

132   that distinguish them from pain of other origins [13]. These pains may be specific to the

133   involvement of a precise anatomical location or a precise organ by the deep endometriosis

134   implants [14]. A detailed clinical history should search for the most common symptoms and

135   their severity, including gynecological symptoms on one side, such as dysmenorrhea [13],

136   cyclical and non-cyclical pelvic pain, deep dyspareunia (and impaired sexual function)[15]

137   and infertility, and non-gynecological cyclical symptoms on the other side, such as dyschezia

138   [16], dysuria [17], hematuria, flank pain, rectal bleeding [14] and shoulder pain [9]. The

139   visual analog scale (VAS) is a well-adapted tool for measuring pain in endometriosis [18].

140   Eventually, physicians should evaluate the potential overall reduction in the quality of life of

141   patients with suspected endometriosis [19,20].

142   <u>Performance of the questioning in women suspected with endometriosis</u>

143   Overall, questioning for each symptom has a high sensitivity, reaching 76–98%, but lacks

144   specificity (20 – 58%) as summarized by Pascoal et al. [21–23]. In a literature review on

145   chronic pelvic pain, Vercellini et al. discussed the frequent non – endometriotic causes, such

146   as irritable bowel syndrome, myofascial syndrome, pelvic adhesions, pelvic venous

147   congestion, and interstitial cystitis [24]. Several authors developed models with different

148 symptoms to predict the presence of endometriosis. Chapron et al. recently [25] identified

149 eight interrogation elements and proposed several diagnostic thresholds for their score:

150 between 1 and ≥ 25: (i) highly specific, correctly identifying patients without the disease; (ii)

151 highly sensitive, identifying the patients with the disease; and (iii) a level maximizing

152 sensitivity and specificity for the best classification of the whole population. They reported

153 the following performance of their model: score 1: specificity of 91% (95% CI [89-93]); score

154 < 11: sensitivity of 91% (95% CI [89-93]); score ≥ 18: specificity of 75% (95% CI [72-78]), and

155 sensitivity of 73% (95% CI [70-76]). Fauconnier et al. reported a standardized self-

156 questionnaire developed from the patients' verbatim (built specifically for diagnosis) with

157 21-item yes/no questions about painful symptoms [26]. They included 105 cases and 197

158 controls, and the full question set prediction model, including age, had an area under the

159 receiver operating characteristic curve of 0.92 (95% confidence interval, 0.87-0.95) after

160 internal validation. The high-risk classification rule had a specificity of 98.0% and a positive

161 likelihood ratio of 30.5. The low-risk classification rule had a sensitivity of 98.1% and

162 negative likelihood ratio of 0.03. Eventually, Bendifallah et al. investigated the use of

163 machine learning algorithms (MLA) in the diagnosis and screening of endometriosis based on

164 16 key clinical and patient-based symptom features [27]. In their work, the sensitivity,

165 specificity, F1-score, and AUCs of the MLA to diagnose endometriosis in the training cohort

166 from the Ziwig Health Platform were 0.82 to 1, 0-0.8, 0-0.88, 0.5-0.89. They performed

167 validation on a 100 – patients prospective cohort with similar performance.

168 Overall, the symptom-based approach is limited by its low specificity and the absence of

169 external validation for most of the models developed. The "paradox" of the aforementioned

170 models is that they were developed in expert centers but aim to increase the diagnostic

171 performance in primary care. Future research could focus on testing their performance in

172 primary care as well as refining their use to help prescribing MRI imaging or guide the

173 patients toward specific pathways of care.

174   Another issue with this approach to diagnose endometriosis is its inability to characterize

175 the extent of the disease, which could have major implications in the decision – making

176 process.

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178

179 <u>Value of the pelvic examination in patients with suspected endometriosis</u>

180   <u>Elements and timing of pelvic examination in women with suspected endometriosis</u>

181 Studies report that between 15% and 30% of women with endometriosis have deep

182 infiltrating disease [13]. Speculum examination may reveal bluish spot characteristic of

183 endometriosis in the retrocervical area and the upper part of the posterior vaginal wall.

184 Vaginal digital examination in women with suspected endometriosis aims to identify deep

185 posterior infiltration of the retrocervical area [28] i.e vaginal nodules vagina (figure 1),

186 uterosacral ligaments, or pouch of Douglas; as well as adnexal masses [29]. One may also

187 palpate induration or nodularity in the anterior area which may be related to deep

188 endometriosis of the bladder or uterine anterior serosa. The painful nature of palpated

189 lesions is characteristic. Pelvic examination also allows the identification of a possible

190 myofascial syndrome [30]. Hypersensitivity phenomenon have been largely documented in

191 women with endometriosis and the association with a myofascial syndrome is frequent, with

192 around 60% of patients having both myofascial syndrome and endometriosis [31]. Allodynia,

193 contact hyperpathia with tight clothing, and provoked vulvodynia should be tested as

194 evidence of cutaneous and vulvar hypersensitivity [32,33]. These patients often have

195 hyperpathy or real trigger points found in the muscles of the perineum or the deep part of

196 the buttocks [34]. Vaginal digital examination can reveal painful tension in the bundles of the

197 levator ani muscle and the pelvic portions of the internal obturator muscles. Painful tension

198 of the piriformis muscles and the gluteal portions of the internal obturator muscles can be

199 sought in the prone position. These pains may be indicative of a regional myofascial

200 syndrome, but are often part of a diffuse pain with extra-pelvic trigger points suggestive of a

201 central hypersensitivity syndrome such as fibromyalgia [35]. These hypersensitization

202 phenomena sustain the pain in patients with endometriosis and explain the persistence of

203 certain pains after surgical management of endometriosis [36]. The myofascial syndrome can

204 also be a differential diagnostic in women with chronic pelvic pain, with no concurrent

205 endometriosis.

206

207

208 Figure 1: bluish endometriosis spots of the posterior vaginal cul de sac

209 Regarding the most opportune moment of physical examination, several studies have shown

210 an improvement in the diagnostic relevance of pelvic examination during menstruation. A

previous study by Koninckx et al. showed a much greater diagnostic performance than during a routine examination outside of menstruation [37]. This better diagnostic performance must be balanced against the discomfort of a pelvic examination during the menstrual period in some women.

As stated in the latest ESHRE guidelines [9], vaginal examinations might be inappropriate in certain situations and in adolescents. Furthermore, it can be painful for some women. In these women, with high burden/discomfort (adolescents, due to religion, painful examination, sexual abuse in the past, virgo intacta, etc.), vaginal examination should ideally be omitted, and other medical technologies, as described below, should be used as a first step towards diagnosis.

Performance of pelvic examination in women with suspected endometriosis

Unlike questioning, clinical examination has a low sensitivity for the diagnosis of endometriosis, and it is therefore well established that a normal clinical examination does not eliminate the diagnosis: more than 50% of patients with laparoscopically proven endometriosis have a normal clinical examination [21]. A recent review by Pascoal et al. reported that the sensitivity and specificity of pelvic examination for the diagnosis of endometriosis were 18 − 88% and 76 − 100%, respectively [23]. The relevance of pelvic examination depends on the locations of endometriosis as highlighted by the work of Bazot et al. [38].

The main performances of pelvic examination according to endometriosis location is detailed in Table 1. The larger cohorts are those of Hudelist et al. reporting on 129 women [39] and the one of Bazot et al. reporting on 92 consecutive women [38]. In this last cohort, the sensitivity, LR + and LR - values of physical examination were, respectively, 73.5%, 3.3,

234 for uterosacral ligament endometriosis; 50%, 3.88, and 0.57, for vaginal endometriosis; and

235 46%, 1.67, and 0.75 for intestinal endometriosis. Eventually, the latest systematic review and

236 meta-analysis by Zhang et al., that included a total of 30 studies with 4,565 participants

237 compared the diagnostic performance of several modalities for endometriosis [40]. Physical

238 examination had a pooled sensitivity of 71% (95% CI, 60‑ 80%) and a specificity of 69% (95%

239 CI, 54‑ 82%), with an average diagnostic accuracy of 0.76 (95% CI, 0.66‑ 0.83).

240   Some studies evaluated the performance of models combining questioning

241 symptoms and pelvic examination signs, increasing the performance of questioning alone

242 models. The study by Chattot et al. established a predictive score for recto sigmoidal

243 involvement comprising 4 parameters including a questioning component (the presence of

244 blood in the stool at the time of menstruation) and a clinical examination component

245 (palpation of a nodule on vaginal touch) [41]. Eskenazi et al. included 90 women with a

246 scheduled laparoscopy or laparotomy [21]. Ultrasound and examination best predicted

247 ovarian endometriosis, correctly classifying 100% of cases with no false positive diagnoses in

248 the study sample.

249   Overall, the value of pelvic examination is conferred by its high positive likehood ratio

250 and specificity. Its performance overpass these of questioning alone for diagnostic purpose.

251 The value of pelvic examination is always compared with that of ultrasound and MRI. The

252 low negative predictive value of "routine" ultrasound for the diagnosis of deep

253 endometriosis has been reported in several studies [38,40,42]: it is relevant mainly for the

254 diagnosis of endometrioma and cannot therefore replace clinical examination. Concerning

255 the value of MRI, the great variability of the MRI protocols described in the literature and

256 the absence of standardized reports limit the reproducibility of this examination in this

257 indication [43]. In addition, the expertise of the radiologist and the location of the lesions

258 (lower agreement for determining damage to the utero sacral ligaments) have an influence

259 on the performance of MRI [44,45]. No study has evaluated the sensitivity and specificity of

260 pelvic MRI for the diagnosis of endometriosis without prior clinical examination.

261   Other benefits of the pelvic examination for the management

262 It is well established that the quality of the preoperative workup influences the quality of

263 surgical excision and minimizes the risk of incomplete excision or an unplanned procedure

264 [46]. Soliman et al 2017 showed that clinical diagnosis (non-invasive) also decreases the time

265 to diagnosis [47]. Similar conclusions were drawn from the recent review by Agarwal et al

266 2019 in the American Journal of Obstetrics and Gynecology (AJOG) [11].

267

268 **Limits**

269 Some bias in the available literature deserves to be underlined, as it could influence the

270 magnitude of the benefit of both medical questioning and pelvic examination. Most

271 published data concern expert centers and clinicians with great experience in diagnosing

272 endometriosis, with an increased prevalence among patients tested when compared to the

273 general population [48].

274 There is also probably a bias linked to the duration of the evolution of symptoms at the time

275 of the consultation and a verification bias inherent in the pathology (the comparator used is

276 always laparoscopy; therefore, only patients with an indication for surgery have formal

277 confirmation of the diagnosis).

278   Furthermore, as underlined in the latest recommendations of the CNGOF – HAS 2018

279 [48], there are no data from the 1st line clinical examination for the diagnosis of deep

280 endometriosis (primary care) since all the studies relate to the performance of examinations

281 by expert - clinicians or highly experienced. In addition, studies are often conducted in

282 "expert" centers, where the prevalence of the disease is probably higher than in the general

283 population. Therefore, it is possible that the diagnostic relevance of clinical examination is

284 overestimated in light of the literature. Eventually, it is possible that the performances of

285 both physical examination and questioning are biased since only patients exhibiting a positive

286 screening test (i.e., intense symptoms and / or positive physical examination) with undergo a

287 laparoscopy to confirm the diagnostic in case of negative or indeterminate imaging. This bias

288 could be responsible for an increased sensitivity and decreased specificity.

289 Another point is that of the bias associated with the duration of the evolution of

290 symptoms at the time of the consultation, which may have implications for the findings of

291 the clinical examination and history and modify their relevance. Finally, there is a verification

292 bias inherent in the pathology and valid for all the studies included; the comparator used is

293 always laparoscopy + / - histological analysis; therefore, only patients with an indication for

294 surgery have formal confirmation (if possible) of the diagnosis.

295 To date, no study has evaluated the diagnostic relevance of history alone compared

296 with pelvic examination alone. No study has assessed the diagnostic relevance of history

297 alone compared with the combination of history and pelvic examination.

298

299

300   **Conclusion**

301   In women with suspected endometriosis, pelvic examination (vaginal speculum and digital

302   vaginal examination) when positive increases the diagnostic value in association with

303   questioning for symptoms. Informing patients on the usefulness of this examination will

304   allow its realization within the framework of an empathetic relationship.

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Author	Type of study	Population included	Intervention	Gold standard	95% CI
Zhang, 2020 [40]	Systematic review and meta - analysis	30 studies including a total of 4565 women.	Physical examination, ultrasound, MRI	Laparoscopy + / - histology	Se 0.71 (0.6 – 0.8) Sp 0.69 (0.54 – 0.82) Diagnostic Odds Radio 5 (3 – 12) LR+ 2.3 (1.5 – 3.6) LR- 0.42 (0.29 – 0.61) AUC 0.76 (0.66 – 0.83) Post-test probability (+ 37%, - 10%) significantly different from the pre-test probability (20%)
Nnoaham, 2012 [16]	Prospective, observational including 19 hospitals in 13 countries	771 women phase I (including 360 with endometriosis) et 625 women phase II (including 364 with endometriosis)	Questionnaires 25 questions	Laparoscopy	Without ultrasound: LR+ 1.5 LR- 0.35 With ultrasound: LR+ 5.39 LR- 0.47
Chapron, 2022 [49]	Case - Controles	2005 - 2018 3 levels of analysis: development cohort (N = 1675 inlcuding 880 with endometriosis), internal validation cohort (N = 842 including 395 with endometriosis) and an external validation cohort (N = 308 including 220 with endometriosis)	Questioning	Laparoscopy	For score 1 >=25 Sp 91% (CI 95% 89 – 93)
Nawrocka-Rutkowska J, 2021 [50]	Prospective cohort	148 women hospitalized in a Polish gynecological department with chronic pelvic pain and at least one symptom suggestive of endometriosis for more than 6 months.	Questioning and physical examination	Diagnostic laparosocpy	The association of "catamenial increased pain and painful sexuel intercourse: Se 63.34%, Sp 65.69%, PPV 12.96% et NPV 95.74%
Bazot, 2009 [38]	Cohort study	92 women with endometriosis	Questioning, physical examination, ultrasound, endorectal ultrasound and MRI	Laparoscopy	For the utero-sacral ligaments, LR+ 3.3 (0,95 – 11.1) and LR- 0.34 (0.22 – 0.58) For the vagina: LR+ 3.88 (1.85 – 8.11) et LR – 0.57 (0.40 – 0.83) For the recto-vaginal pouch, LR+ 4.91 (0.92 – 26.2) et LR- 0.85 (0.64 – 1.13) For digestive lesions, LR+ 1.67 (0.87 – 3.19) and LR – 0.75 (0.54 – 1.03)
Arion, 2019 [51]	Data from a prospective cohort	269 women incluing 41 with Douglas pouch with endometriosis	Physical examination	Endovaginal ultrasound « sliding sign »	Se 0.24 (0.12 – 0.40) Sp 0.93 (0.89 – 0.96) PPV 0.40 (0.24 – 0.58) NPV 0.87 (0.85 – 0.89) LR+ 3.7 (1.8 – 7.7) LR- 0.81 (0.68 – 0.97)
Lafay Pillet, 2014 [52]	Cohort study	326 women with ovarian endometriosis operated between january 2005 and octobre 2011 : 164 with deep infiltrating endometriosis and 162 without deep infiltrating endometriosis. patientes avec endométriome opérées entre Janvier 2005 et Octobre 2011 : 164 avec endométriose profonde et 162 sans endométriose profonde	Questioning	Laparoscopy + / - histology	No LR+/- on the VAS except for urinary pain LR + = 4
Fauconnier, 2021 [26]	Prospective case – controls	105 with endometriosis and 197 controls with no endometriosis	Questionnaire ENDOPAIN-4D.	Laproscopy + / - histology	LR+ 30.5 / LR- 0.03 With pre-test prevalence of 10%, post-test + 77.2% / - 0.3%
Fedele, 2007 [53]	Cohort study	157 women operated with chronic pelvic pain including 127 with endometriosis and 14 bladder endometriosis. The objective was to predict bladder endometriosis.	Questionnaire American Urologic Association Symptom Index modified partially	Laparoscopy or laparotomy	With a threshold set at 9, max Se (93%) and Sp (88%)

Hudelist, 2009 [54]	Prospective cohort	200 consecutive women with symptoms suggestive of endometriosis. Eventually, 135 cases (68%) of endometriosis.	Questioning, physical examination and ultrasound	Laparoscopy + / - histology	Physical examination alone Sp 89 – 100% Se 23 – 88%, PPV 65 – 100%, NPV 85 – 99%, Accuracy 86 – 99%. Physical examination and endovaginal ultrasound Se 67 – 100%, Sp 86 – 100%, PPV 50 – 100%, NPV 93 – 100, Accuracy 86 – 100%

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