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1 **Do women with suspected endometriosis benefit from pelvic examination to improve**
2 **diagnostic and management strategy?**

3
4 Yohann DABI^{1,2}, Arnaud FAUCONNIER^{3,4}, Christine ROUSSET-JABLONSKI^{5,6,7}, Arounie
5 TAVENET⁸, Anne-Cécile PIZZOFFERRATO⁹, Xavier DEFFIEUX¹⁰

- 6
7 1. Sorbonne Université, Hôpital Tenon, Service de Gynécologie Obstétrique et Médecine
8 de la Reproduction, Assistance Publique des Hôpitaux de Paris, Paris.
9 2. Groupe de Recherche Clinique 6 (GRC6), Centre Expert Endométriose (C3E), Sorbonne
10 Université.
11 3. *Université Paris-Saclay, UVSQ, Unité de recherche 7285 Risques cliniques et sécurité*
12 *en santé des femmes et en santé périnatale, Montigny-le-Bretonneux, France*
13 4. Université Department of Obstetrics and Gynecology, intercommunal Hospital of
14 Poissy / Saint-Germain-en-Laye, Poissy, France
15 5. Département de chirurgie, Centre Léon Bérard, Lyon
16 6. Service de Gynécologie Obstétrique, Centre Hospitalier Lyon Sud, Pierre Bénite
17 7. INSERM U1290 RESHAPE, Université Claude Bernard Lyon 1, Lyon
18 8. Endofrance, Association de lutte contre l'endométriose, 3, rue de la Gare, 70190
19 Tresilley, France
20 9. Faculté de Médecine et Pharmacie, Université de Poitiers, Inserm CIC 1402, Service
21 de Gynécologie-Obstétrique et Médecine de la Reproduction, CHU de Poitiers,
22 Poitiers.
23 10. Université Paris Saclay; Service de gynécologie obstétrique, hôpital Antoine Bécclère,
24 APHP, Clamart , F-92140 (France)

25
26
27 ***Conflicts of interest :***

28 *AF déclare avoir des liens d'intérêt suivants : SELAS Pointgyn, Laboratoire Innotech*
29 *International, Respiratory and Women's Health Products, le Center for observational and*
30 *real-world evidence (CORE)*

31 *CRJ déclare être consultante pour Bristol Myers Squibb, Novartis, Organon,, Roche,*
32 *Theramex ;*

33 *XD déclare être actionnaire de Sanofi et Nanobiotix, être expert pour la HAS et le Haut*
34 *conseil pour la nomenclature et consultant pour Astellas, Coloplast, Hologic, IBSA Pharma,*
35 *Laborie, Mylan, Pierre-Fabre et être auteur pour Elsevier-Masson, Regimedia et*
36 *HealthEvents ;*

37 *YD déclare avoir des liens d'intérêts avec la SELAS PointGyn.*

38
39 **Corresponding author:**

40 *Yohann DABI*

41 *Sorbonne University, Tenon Hospital, Department of Obstetrics and Gynecology, AP-HP*
42 *Postal adresse: 4 rue de la Chine, 75020, Paris, France*

43 *E-mail : yohann.dabi@gmail.com*

44 *Tel : 01 56 01 70 00*

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 likelihood

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

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

108 **Methods**

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

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

123

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 Value of the questioning for symptoms in the diagnostic strategy of patients with suspected
128 endometriosis

129 Elements of the systematic questioning in women with suspected endometriosis

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 Performance of the questioning in women suspected with endometriosis

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.

177

178

179 Value of the pelvic examination in patients with suspected endometriosis

180 Elements and timing of pelvic examination in women with suspected endometriosis

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

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

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

221 Performance of pelvic examination in women with suspected endometriosis

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

230 The main performances of pelvic examination according to endometriosis location is
231 detailed in Table 1. The larger cohorts are those of Hudelist et al. reporting on 129 women
232 [39] and the one of Bazot et al. reporting on 92 consecutive women [38]. In this last cohort,
233 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 likelihood 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 Ratio 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%) Without ultrasound: LR+ 1.5 LR- 0.35 With ultrasound: LR+ 5.39 LR- 0.47
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 including 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 \geq 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 laparoscopy	The association of "catamenial increased pain and painful sexual 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 including 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 October 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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