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Original Article

A self-administered questionnaire to measure the painful symptoms of endometriosis: Results of a modified DELPHI survey of patients and physicians

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ABSTRACT

Purpose. – To develop a questionnaire based on patients' verbal descriptors, to measure the painful symptoms of endometriosis.
Methods. – We performed a two-round modified DELPHI procedure mixing endometriosis patients and physicians to select a set of statements to describe the painful symptoms of endometriosis. Each panelist rated each statement based on diagnosis validity and clarity. The clinicians were experts in endometriosis management selected from various geographic regions in France. Patients were women with surgically confirmed endometriosis who volunteered from a patient association and from the recruitment of the participating physicians. The first round questions were derived from words and phrases in narratives of pain by endometriosis patients.
Results. – Overall, 76 experts were invited, and of these 56 (74%), comprising 33 patients and 23 gynecologists, responded to the first round questionnaire, and 40 (71.4%) to the second round. Among the 48 statements assessed in the first-round questionnaire, 11 were selected after completion of the two round DELPHI procedure. After discussion and rewording of some items, a total of 21 questions were selected during a final face-to-face meeting. The content of the final questionnaire is organized according to four dimensions: (i) spontaneous pelvic pain and dysmenorrhea, (ii) dyspareunia, (iii) painful bowel symptoms, (iv) and other symptoms. We also provide an English (UK) version produced using several steps of translation and back-translation.
Conclusions. – The questionnaire has content validity to measure the subjective experiences of patients with painful endometriosis and can provide a solid basis on which to develop an efficient patient-centered outcome to measure the painful symptoms in therapeutic or in diagnostic studies of endometriosis.

Introduction

Endometriosis is a painful chronic disease affecting about 10% of women in Organisation for economic co-operation and development (OCDE) countries [1]. Endometriosis is responsible

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for various pelvic pain symptoms [2] that can have a great impact on all aspects of the life of endometriosis patients [3].

Measuring pain symptoms and Health-related quality of life (HrQol) in endometriosis patients was useful to assess treatment outcome in clinical trials including medical therapy, or surgery [4,5]. Various methods of pain assessment are available in the context of endometriosis, some of which have been validated with a high level of evidence. The visual analog scale (VAS) and the numerical rating scale (NRS) are the most frequently used pain scales to assess each type of typical pain related to endometriosis (dysmenorrhea, deep dyspareunia and non-menstrual chronic pelvic pain). Although these scales are appropriate for the measurement of the individual pain symptoms [6], they do not take into account the heterogeneity of the painful symptoms of endometriosis. Furthermore, each of the pain symptoms that may relate to endometriosis involves numerous distinct descriptors and there was considerable variability in symptom description and interpretation by patients and by physicians [7].

Therefore, there is a need for reliable and well-defined patient-reported outcome measures (PRO's) that can be used to determine the clinical benefit of medical interventions and/or promote early diagnosis of endometriosis [8]. Important efforts have been made to develop and validate HrQol questionnaire in the context of endometriosis, see for example SF-36 [9], or The "Endometriosis Health Profile 30" (EHP-30), specially developed to capture the impact of endometriosis on specific domains of HrQol [10]. Although endometriosis symptom questionnaires have already been used in an epidemiological surveys [11] and in clinical studies [12], to the best of our knowledge, the various existing pain questionnaires and pain scales to assess symptoms related to endometriosis were primarily developed on the basis of clinician input. Currently, there are few data on the patients' descriptions of symptoms and at the present time, no questionnaire is available to obtain data from patients.

In a previous study, by analyzing in-depth interviews with endometriosis patients, we identified numerous verbal descriptors representing the patients' experience [7]. Here, we describe a first-step questionnaire development based on these verbal descriptors to measure the chronic pain symptoms of endometriosis using a PRO's approach. To achieve this, consensus needs to be reached among the various stakeholders involved in the care of women with endometriosis as well as patient representatives. The aim was to select a set of relevant statements based on patients' perception of painful symptoms to construct a short, standardized self-administered questionnaire.

Methods

We conducted a two-round modified DELPHI survey among a multidisciplinary expert panel comprising endometriosis patients and physicians, whether gynecologists or not, involved in the diagnosis and treatment of endometriosis. The Delphi method is a practical and structured method to achieve a convergence of opinion and a general consensus on a particular topic from a large number of individuals. It has been used to develop medical recommendations clinical guidelines, questionnaire or clinical indicators such as indicators reflecting patient and general practitioner perceptions of chronic illness. The participants take part anonymously in sequential questionnaires that constitute different rounds [13]. The panellists rate the statements, and statements made by participants at each round of the process can be used to formulate the next round of questions. For the purpose of the present study, we used a modified Delphi technique in which questionnaire rounds were followed by a physical meeting of the panellists, to enhance the complex decision-making process and to clarify the language used to describe each statement [14].

Pre-selection of statements

First round questionnaire statements were developed from previous qualitative research [7]: The statements were based on the fully-comprehensive descriptions of painful symptoms obtained by qualitative, interview-based study and analyzed using Colaizzi's method [15], with endometriosis patients selected to represent different types of endometriosis (i.e. superficial endometriosis, ovarian endometriosis, or deeply infiltrating endometriosis [DIE]). To ensure a proper formulation of the first round statements, we first designed an in-person focus group discussions with eights subjects with endometriosis and interested in describing the word of pain (these subjects were not further involved in the DELPHI). The discussion was centered on the meaning of the words and sentences used to describe endometriosis pain related symptoms in order to reformulate some of the items and to clarify some of the sentences used. No physician was present at the time of the focus group discussion. The participating women also recommended to add two themes "fears from sexual intercourse because of the pain" #26 and "difficulties to get pregnant". In total, 48 statements were identified and were used for the first round questionnaire. These statements fall into five general categories:

- severe pelvic pain and dysmenorrhea ($n = 21$);
- dyspareunia ($n = 6$);
- gastro-intestinal symptoms ($n = 8$);
- painful urinary tract signs ($n = 6$);
- other symptoms ($n = 7$).

Panel members

To form a representative expert panel, the aim was to gather a heterogeneous group in order to ensure that the broadest spectrum of opinion was obtained. The clinicians were recognized French-speaking experts in endometriosis including gynecologist surgeons, specialists in reproductive medicine and specialists in pelvic imaging. They were selected from various geographic regions within France and Belgium, and were in practice in university teaching hospitals, general hospitals or in private centers to ensure that they represented a wide array of clinical approaches, backgrounds and practices. The panelists were also selected to represent a broad range of age and experience levels. Endometriosis patients were volunteers diagnosed with endometriosis by surgery; the patients came from a French association of patients with endometriosis (Endofrance, http://www.endofrance.org/) and from the recruitment of the participating physicians. We planned to include about 30 panelists by stakeholder category (i.e. physicians and patients).

First round

The panelists who agreed to participate received the first questionnaire by e-mail. Non-responders were re-contacted by e-mail and telephone. Each panelist was invited to rate the 48 statements for two aspects:

- diagnosis validity, i.e. the statement had the appropriate characteristics to effectively diagnose endometriosis, it appeared to be sufficiently sensitive and/or specific to help detect endometriosis patients from patients with other diseases or free of any pathology;

- clarity, i.e. the statement is expressed in clear, precise and unambiguous terms for both clinicians and patients.

Diagnosis validity and clarity were each rated on a 9-point scale, where 1 meant definitely not valid or not clear and 9 definitely valid or clear statements. The questionnaire also invited the panelists to comment on each of the statements and to suggest additional statements not included in the list.

The central tendency was based on the median of the ratings and agreement among panelists expressed as a percentage. We selected statements for which a consensus was achieved regarding diagnosis validity and clarity: i.e. for which the median score was in the top tertile (7–9) and at least 65% of panel ratings were in the top tertile, for both diagnosis validity and clarity.

If consensus was achieved regarding diagnosis validity only, the statement could be rephrased according to the panelists' comments and proposed for rating in the second round. At the end of the first round, the questionnaire was modified and some statements were added or modified to take the panelists' comments and suggestions into account. When the experts' comments seem relevant, deleted statements were either modified or added in the second round without any modification.

Second round

Each of the panelists who had participated in the first round was sent the second-round questionnaire by mail. These panelists were also given feedback on the results of the first round (median panel rating for diagnosis validity and for clarity, frequency distribution and their individual ratings). They were asked to re-rate each statement based on both their own opinion and the panel responses obtained during the first round. To be included in the final set, statements had to have median diagnosis validity and clarity ratings in the top tertile (7–9) and 75% agreement among panelists that the rating was in the top tertile [14]. We also compared patients' and practitioners' responses in term of statements selected.

Face-to-face meeting

All panel members were invited for this consensus meeting during which an overview of the results of the second round ratings was provided. The meeting was chaired by three of the authors (A.F., S.S. and R.B.). Results of the second round were discussed to identify areas of disagreement. This meeting also allowed clarification or rephrasing of accepted statements.

Translation into English of the final set of questions

The translation was performed according to previously published guidelines [16]. Three native English-speaking women, bilingual in French, involved in the field of gynecology translated the French version into an English draft version. Together, the translators consolidated their translations into a single first English version. Then, three French native bilingual health-care providers experienced in gynecology, back-translated this first version into French (without having seen the original French version). The three initial translators then reviewed the three back-translation against the original English version, and provided a final forward translation.

Results

Seventy-six patients and obstetricians/gynecologists were invited to be part of the DELPHI expert panel. The panel thus consisted of 40 obstetricians/gynecologists and 36 patients. Among them, 56 (74%) responded to the first round questionnaire. Of these, 33 were patients and 23 were obstetricians/gynecologists (all listed in alphabetic order in the "Acknowledgment" section). Table 1 reports the main characteristics of the panelists who responded to the first round questionnaire.

Fig. 1 shows the workflow of statements that were included, deleted or suggested in each of the two rounds and the face-to-face meeting. The final results with levels of agreement in the two rounds are presented in Table 2.

The first round was performed from 15th January 2014 to 13th October 2014. "#2: very painful menstruation" and "#29 pain when passing a stool, painful bowel movements" had the diagnosis validity ratings with the strongest agreement (respectively 93% and 83.3%). "#31: diarrhea during menstruation" had the clarity ratings with the strongest agreement (96%). Twenty-three percent of statements reached the first level of consensus (11/48). Among these 11 statements, only 4 were not modified ("#2: very painful menstruation", "#24: pain in certain positions during sexual intercourse", "#25: deep internal pain felt during sexual intercourse" and "#49: difficult to get pregnant"). One statement "#22: strong, sharp pain during sexual intercourse" was discarded because it was merged with "#23: distracting pain that prevents or interrupts sexual intercourse" (Table 2). Twenty other statements were discarded (42%) because they didn't reach the required level of consensus. 16/48 (33%) statements didn't reached consensus level but were maintained based on the feedback from the participants. Modifications were made to 11 of these statements (Table 2). One new statement was added (need to strain to start passing water, difficult to empty the bladder completely, especially during menstruation), producing 28 statements to be rated for the second round.

The second round was conducted between November 11, 2014 and April 01, 2015. It was completed by 40 (40/56: 71%) panelists. Of these, 20 (50%) were patients and 20 (50%) were clinicians. At this step of the process, 28 statements were therefore evaluated, including modified, retained or additional statements. The panel selected 11/28 (39%) of statements as valid. Among these "# 24: pain in certain positions during sexual intercourse" and "#29: pain when passing a stool. Bowel movements are painful during menstruation" again showed the strongest agreement for diagnosis validity (respectively 100% and 94.4%). Seventeen statements were discarded. Among these, 12 were the subject of a difference in opinion between patients and physicians, i.e. the obstetricians/gynecologists discarded all of them while patients retained all of them (Table 3).

Table 1
Characteristics of the panelists.

Characteristic	*n*	Median (Q1–Q3)	%
Total participants	56		
Female	38		68
Male	18		32
Patients	33		
Physician-based recruitment	15		45
Association-based recruitment	18		55
Age of patient, years (range)		35 (31–37)	
Mean time since diagnosis, years (range)		2 (1–4)	
III-IV stage	19		58
Intestinal endometriosis	7		21
Physicians[a]	23		
Age of physician, years (range)		49 (44–57)	
Years of practice (range)		18 (11–29)	
Practice location			
Teaching hospital	14		61
Non-teaching hospital	3		13
Private practice	6		26

[a] Twenty-two were gynecologists and one a radiologist.

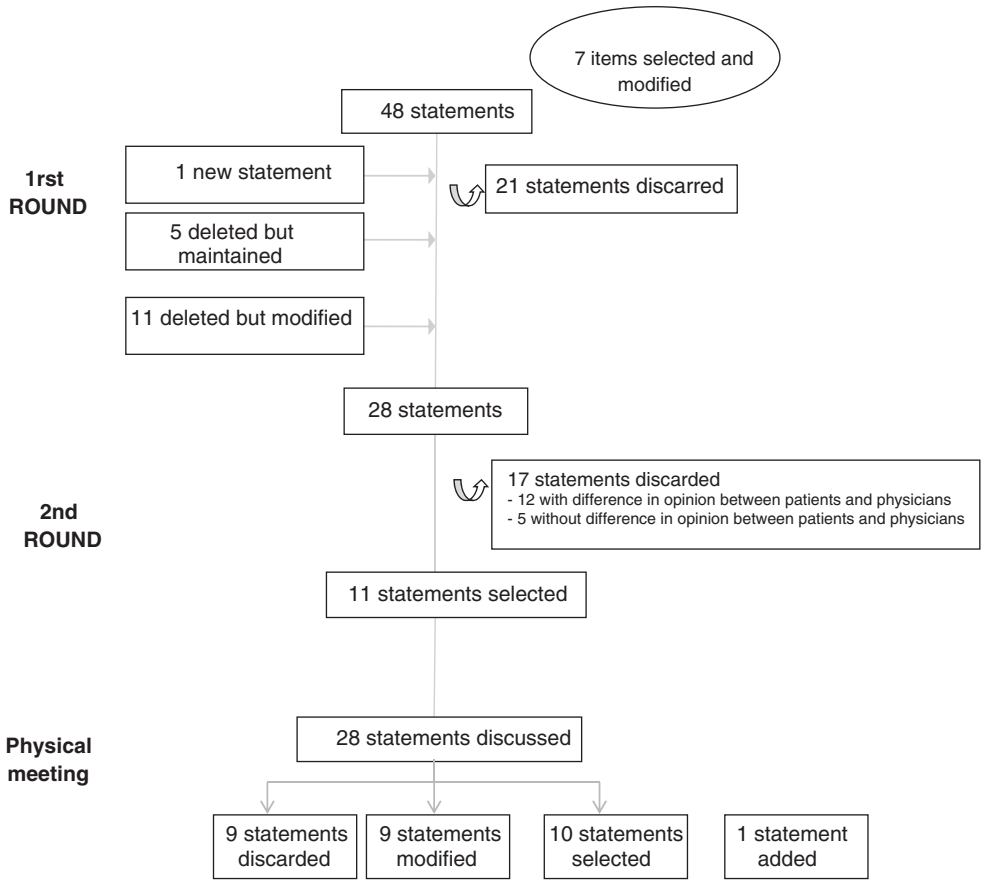

Fig. 1. Flow chart of statements.

Face-to-face meeting

During the physical meeting, 3 patients and 6 obstetricians/gynecologists were present. They first discussed the 11 statements that were selected in the second round. All were accepted but some modifications were made to improve face and content validity for 6 of them: for example "# 2: very painful menstruation" was replaced by "pain located in the lower abdomen during menstruation", "# 25: deep internal pain felt during sexual intercourse" into "Intense, sharp pain deep inside during sexual intercourse". For painful bowel signs, the term "during menstruation" was replaced by "especially (worse) during menstruation" (Table 2). Secondly, the 12 statements where patients and physicians did not agree (Table 3) were discussed. Of these, 6 were definitively discarded, mostly because they did not provide useful information at the medical level and/or may have multiple interpretations (i.e. "# 15: pain located in the ovaries", "# 14: uterine cramps", or "# 34: Bloating, bloated abdomen during menstruation"). Conversely, four among these statements were finally re-instated because the practitioners and the patients agreed that these statements, although they were not discriminant for the diagnosis of endometriosis, they reflected well the perception that the patients had of their pain symptoms: "# 6: Pain starts a few days before menstruation begins and continues for a few days after menstruation has stopped"; #17: the pain spreads to your back, in the lower back area"; "#18: the pain spreads to the legs and hips; "# 20: pain makes standing, walking or moving difficult if not impossible". Two statements were reformulated: "# 1: pain located in the lower abdomen" became "Pain located in the lower abdomen, outside the menstrual period" and "# 31: diarrhea during menstruation" became "Diarrhea and/or constipation especially (worse) during menstruation". Two statements regarding painful urinary tract signs that were discarded during the first round, "# 36: the urge to urinate is painful, pain when urinating especially during menstruation" and "# 42: need to strain to start passing water, difficult to empty the bladder completely, especially during menstruation" were merged into "difficulty and/or pain when urinating especially during menstruation". One statement "#43: sciatica during menstruation", also discarded during the first round, was added after discussion by the panelists present at the meeting, producing 20 statements definitively selected (Table 2).

Participants were also asked to choose the means of response between several proposals for the self-administered questionnaire based on the selected statements. They pointed out that some questions (eg: # 6 or # 18) naturally call for a yes or no binary answer, whereas other questions that would give rise to a numerical intensity response. In order to make all the questions homogeneous and to allow establishment of scores in the future it was decided to choose a mixed method including a binary answer in "Yes" or "No" followed with a rating of the symptom by 11-point NRS, including 0. As some of the painful symptoms were found to vary across the time, it was decided to provide two distinct NRS to describe the pain intensity of the symptom on average, and at it worst moment.

The final questionnaire was then assessed in a pilot study of 18 endometriosis patients who filled out a first draft version ($n = 6$) and then a final version ($n = 12$) of the questionnaire. During the test phase of the questionnaire, the first version underwent several minor modifications to increase comprehension and feasibility. The second and definitive version was well accepted. Following remarks made by two patients, with documented bladder

Table 2
Results of round 1, 2 and panel physical meeting concerning the 48 statements scored in the first round.

	Round 1				Round 2				Physical meeting	
#	Item	Diagnosis validity	Clarity	Status	Modification	Diagnosis validity	Clarity	Status	Status	Modification
Pelvic pain and dysmenorrhea										
1	Lower abdominal pain	7 (54.5)	8 (77.8)	Modified	Pain located in the lower abdomen	7 (57.9)	8 (83.8)	Discarded but discussed	Modified	Pain located in the lower abdomen, outside the menstrual period
2	Very painful menstruation	9 (92.8)	9 (94.2)	Retained		9 (91.9)	9 (100)	Selected	Modified	Pain located in the lower abdomen during menstruation
3	Pain that is intense, overwhelming, violent, unbearable	8 (64.2)	8 (72.7)	Modified	The pain is very intense; it is violent, obtrusive, unbearable	8 (76.3)	8 (78.4)	Selected	Selected	
4	The pain increases in intensity over time	7 (66.1)	8 (72.7)	Modified	As the years go by, the pain gets worse with time	7 (86.8)	8 (89.2)	Selected	Selected	
5	The pain lasts longer than menstrual pain, and continues after the bleeding has stopped	7 (55.4)	8.5 (79.6)	Discarded		/	/	/		
6	Pain starts a few days before menstruation begins	7 (50.9)	9 (90.4)	Modified	Pain starts a few days before menstruation begins and continues for a few days after menstruation has stopped	7 (63.2)	9 (94.4)	Discarded but discussed	Selected	
7	Pain before, during and after menstruation	7 (54.5)	9 (83.0)	Discarded		/	/	/		
8	Pain depends on the time of the monthly cycle	7 (52.7)	7 (57.4)	Discarded		/	/	/		
9	Pain throughout the monthly cycle, present all the time	6 (47.3)	8 (77.8)	Discarded		/	/	/		
10	Continuous pain with peaks or attacks of more intense pain	7 (56.4)	8 (72.2)	Discarded but maintained		7 (68.4)	8 (86.1)	Discarded but discussed	Discarded	Redundant with item #11
11	Stabbing pain	9 (83.0)	7 (59.2)	Modified	The pain comes by fits and starts, a stabbing pain	8 (72.9)	8 (75.7)	Selected	Selected	
12	Prickly pain, like being pricked or having an injection	5 (27.8)	8 (69.8)	Discarded		/	/	/		
13	Lower abdominal burning pain	5 (31.5)	8 (71.7)	Discarded		/	/	/		
14	Uterine cramps	6.5 (50.0)	8 (66.7)	Discarded but maintained		6 (40.5)	8 (70.3)	Discarded but discussed	Discarded	
15	Ovarian pain	7 (57.4)	8 (61.5)	Modified	Pain located in the ovaries	6 (45.9)	8 (69.4)	Discarded but discussed	Discarded	
16	Pain on one side, pain stronger on one side	6 (40.7)	8 (77.3)	Discarded		/	/	/		
17	Pain spreads towards the back	7 (53.8)	9 (75.5)	Modified	Pain spreads towards the back, in the lumbar area	7 (56.8)	9 (86.5)	Discarded but discussed	Selected	
18	Pain spreads to the legs and hips	7 (50.9)	9 (76.9)	Discarded but maintained		7 (57.1)	9 (88.9)	Discarded but discussed	Selected	
19	Different types of pain at the same time, several different pain symptoms	7 (52.8)	7 (54.9)	Discarded but maintained		6 (48.6)	7 (58.3)	Discarded but discussed	Discarded	
20	Paralyzing, handicapping pain that affects mobility, difficulty walking	6 (49.1)	8.5 (73.1)	Modified	Pain makes standing, walking or moving difficult if not impossible	7 (55.6)	9 (88.6)	Discarded but discussed	Selected	

Table 2 (*Continued*)

#	Round 1				Round 2				Physical meeting	
	Item	Diagnosis validity	Clarity	Status	Modification	Diagnosis validity	Clarity	Status	Status	Modification
21	Pain interferes with daily life	9 (79.2)	9 (86.5)	Modified	Pain makes normal daily activities difficult or impossible	8 (77.8)	9 (97.2)	Selected	Selected	
Dyspareunia										
22	Strong, sharp pain during sexual intercourse	7.5 (67.3)	9 (80.4)		Discarded		/	/	/	
23	Distracting pain that prevents or interrupts sexual intercourse	8 (73.6)	9 (90.2)	Modified	Intense, sharp and disruptive pain, preventing or interrupting sexual intercourse	8 (78.4)	9 (97.1)	Selected	Modified	The pain interferes with, prevents or interrupts sexual intercourse
24	Pain in certain positions during sexual intercourse	8 (81.1)	9 (94.2)	Retained		8 (100)	9 (100)	Selected	Selected	
25	Deep internal pain felt during sexual intercourse	8 (80.8)	9 (90.0)	Retained		8 (89.2)	9 (100)	Selected	Modified	Intense, sharp pain deep inside during sexual intercourse
26	Nervous about having sexual intercourse because of the pain	8 (65.4)	9 (86.0)	Modified	Nervous about having sexual intercourse because of the pain, vaginismus	8 (54.0)	8 (77.8)	Discarded but discussed	Discarded	
27	Burning feeling during or after sexual intercourse	5 (37.8)	9 (76.5)	Discarded		/	/	/		
Painful bowel signs										
28	Anal pain	5 (37.0)	9 (78.4)	Discarded		/	/	/		
29	Pain when passing a stool, painful bowel movements	8 (83.3)	9 (94.0)	Modified	Pain when passing a stool. Bowel movements are painful during menstruation	8.5 (94.4)	9 (100)	Selected	Modified	Pain when passing a stool. Bowel movements painful especially (worse) during menstruation
30	Spasms, cramp, pain in the bowel before having a bowel movement	8 (61.1)	9 (81.1)	Modified	Spasms, cramp, pain in the bowel before having a bowel movement during menstruation	8 (75)	9 (94.3)	Selected	Modified	Spasms, cramp, pain in the bowel before having a bowel movement especially (worse) during menstruation
31	Diarrhea during menstruation	7 (59.3)	9 (96.2)	Discarded but maintained		8 (70.3)	9 (97.1)	Discarded but discussed	Modified	Diarrhea and/or constipation especially (worse) during menstruation
32	Diarrhea alternating with constipation	6.5 (50.0)	9 (84.3)	Discarded		/	/	/		
33	Constipation during menstruation	6 (49.1)	9 (86.5)	Discarded		/	/	/		
34	Bloating, bloated abdomen	7 (51.8)	9 (76.9)	Modified	Bloating, bloated abdomen during menstruation	7 (59.5)	9 (88.9)	Discarded but discussed	Discarded	
35	Bloody stools	7 (52.8)	9 (92.4)	Discarded		/	/	/		
Painful urinary tract signs										
36	Pain or burning when urinating	4.5 (25.9)	9 (84.9)	Modified	The urge to urinate is painful, pain when urinating especially during menstruation	6 (48.6)	9 (97.1)	Discarded but discussed	Modified	Difficulty and/or pain when urinating especially during menstruation
37	Pain with urge to urinate, pain when holding back	5 (37.0)	9 (77.3)	Discarded		/	/	/		

Table 2 (*Continued*)

#	Round 1				Round 2				Physical meeting	
	Item	Diagnosis validity	Clarity	Status	Modification	Diagnosis validity	Clarity	Status	Status	Modification
38	Painful pressure on the bladder	5 (36.5)	8 (65.3)	Modified	Pain in the bladder, especially during menstruation	6 (41.7)	8 (73.5)	Discarded but discussed	Discarded	
39	Difficult to start urination	4 (32.1)	9 (83.7)	Discarded		/	/	/		
40	Feeling the need to urinate often, only small quantities at a time	4.5 (33.3)	9 (84.3)	Discarded		/	/	/		
41	Bloody urine	5 (37.2)	9 (88.5)	Discarded		/	/	/		
42				Added[a]	Need to strain to start passing water, difficult to empty the bladder completely, especially during menstruation	7 (52.6)	8.5 (88.9)	Discarded but discussed	Discarded	
Other signs										
43	Sciatica during menstruation	7 (53.7)	8 (65.4)	Discarded				/	Rehabilitated	Sciatica during menstruation
44	Pain in the right shoulder	5 (38.9)	8 (71.1)	Modified	Pain in the right shoulder or below the right rib cage during menstruation	6 (48.6)	8 (87.9)	Discarded but discussed	Selected	
45	Pneumothorax – air between the lung and chest wall causing chest pain	3 (28.3)	7 (51.9)	Discarded		/	/	/		
46	Nausea, vomiting	5 (38.5)	9 (83.0)	Discarded		/	/	/		
47	Dizziness, fainting	5 (37.7)	9 (80.8)	Discarded		/	/	/		
48	Becoming increasingly tired, extreme exhaustion, slowing down	8 (59.3)	9 (86.5)	Modified	Extreme fatigue, total exhaustion which interferes with daily life	7 (51.4)	9 (86.1)	Discarded but discussed	Discarded	
49	Difficult to get pregnant	9 (75.0)	9 (90.0)	Retained		8 (80)	9 (88.9)	Selected	Modified	Difficult to get pregnant, failure to conceive after several months or years of trying

[a] Statement was added after first round.

Table 3
Twelve items with discrepancy between opinions of the patients and physicians in round 2.

Statements	Diagnosis validity		Clarity		Status after 2nd round	Final status after discussion
	Median	% agreement (7–9)	Median	% agreement (7–9)		
#1: pain located in the lower abdomen	**7**	**55.3**	**8**	**83.8**	**Discarded**	**Retained but modified**
Patients	*8*	*88.9*	*9*	*88.2*	*Retained*	
Physicians	*5.5*	*25*	*8*	*80*	*Discarded*	
#6: pain starts a few days before menstruation begins and continues for a few days after menstruation has stopped	**7**	**63.2**	**9**	**94.4**	**Discarded**	**Selected**
Patients	*8.5*	*94.4*	*9*	*100*	*Retained*	
Physicians	*6*	*35*	*9*	*89.5*	*Discarded*	
#10: continuous pain with peaks or attacks of more intense pain	**7**	**68.4**	**8**	**86.1**	**Discarded**	**Discarded because redundancy**
Patients	*9*	*88.9*	*9*	*93.7*	*Retained*	
Physicians	*6.5*	*50*	*8*	*80*	Discarded	
#14: uterine cramps	**6**	**40.5**	**8**	**70.3**	**Discarded**	**Discarded**
Patients	*8*	*76.5*	*9*	*82.3*	*Retained*	
Physicians	*5.5*	*10*	*7*	*60*	*Discarded*	
#15: pain located in the ovaries	**6**	**45.9**	**8**	**69.4**	**Discarded**	**Discarded**
Patients	*8*	*82.3*	*9*	*100*	*Retained*	
Physicians	*5*	*15*	*6*	*42.1*	*Discarded*	
#17: pain spreads towards the back, in the lumbar area	**7**	**56.8**	**9**	**86.5**	**Discarded**	**Selected**
Patients	*8*	*82.3*	*9*	*100*	*Retained*	
Physicians	*6*	*35*	*8*	*75*	*Discarded*	
#18: pain spreads to the legs and hips	**7**	**57.1**	**9**	**88.9**	**Discarded**	**Selected**
Patients	*8*	*76.5*	*9*	*100*	*Retained*	
Physicians	*6*	*38.9*	*8*	*78.9*	*Discarded*	
#19: different types of pain at the same time, several different pain symptoms	**6**	**48.6**	**7**	**58.3**	**Discarded**	**Discarded**
Patients	*8*	*77.8*	*9*	*76.5*	*Retained*	
Physicians	*5*	*21.1*	*6*	*42.1*	*Discarded*	
#20: pain makes standing, walking or moving difficult if not impossible	**7**	**55.6**	**9**	**88.6**	**Discarded**	**Selected**
Patients	*9*	*88.2*	*9*	*100*	*Retained*	
Physicians	*4*	*26.3*	*8*	*78.9*	*Discarded*	
#31: diarrhea during menstruation	**8**	**70.3**	**9**	**97.1**	**Discarded**	**Retained but modified**
Patients	*8*	*82.3*	*9*	*93.7*	*Retained*	
Physicians	*7*	*60*	*8*	*100*	*Discarded*	
#34: bloating, bloated abdomen during menstruation	**7**	**59.5**	**9**	**88.9**	**Discarded**	**Discarded**
Patients	*8*	*88.2*	*9*	*100*	*Retained*	
Physicians	*5*	*35*	*8*	*80*	*Discarded*	
#48: extreme fatigue, total exhaustion which interface with daily life	*7*	*51.4*	*9*	*86.1*	**Discarded**	**Discarded**
Patients	*9*	*88.2*	*9*	*100*	*Retained*	
Physicians	*6*	*20*	*8*	*75*	*Discarded*	

Bold results represent results of all the panel (patients + physicians), and in *italic* the results splitted according the statut of the pannelist.

endometriosis and who expressly described the symptom, we introduced a new question "Pain in the bladder, when you want to urinate, or when holding back, especially during your period" was finally re-introduced based on questions # 37 and 38 (Table 2). The French final version is available in supplementary material. The final English version is given in Appendix.

Discussion

We provide a brief (21 statement) self-assessed questionnaire to measure specifically the painful symptoms of endometriosis. The questions were derived from words and phrases in narratives of pain from endometriosis patients and selected by a panel of patients and physicians to specifically represent accurate descriptors of endometriosis pain symptoms but are also useful from a medical point of view. The content of the questionnaire is displayed according to four dimensions: spontaneous pelvic pain and dysmenorrhea, dyspareunia, painful bowel symptoms, and other symptoms, that may reflect the heterogeneity of the painful experience of endometriosis. The set of questions and their means of response enable one or several aggregated indexes to be constructed to characterize the pain of endometriosis for use as a PRO.

Our model addresses the difficulties encountered in measuring pain in endometriosis patients. First of all, the pain symptoms are heterogeneous among patients, which is problematic when using pain as an outcome. In an earlier randomized controlled trial (RCT), comparison of the effects of medroxyprogesterone acetate to danazol and placebo involved six distinct before and after measurement pain scores: pelvic pain, lower back pain, defecation pain, dysuria, dyspareunia, and diarrhea. By chance most of these symptoms were very sensitive to the treatments effects [17]. Conversely, the difficulties were more obvious in one RCT comparing excisional laparoscopic surgery to placebo for the treatment of painful endometriosis [5]. Although surgery appeared to be efficient for pain, it was not possible to discriminate the effect of surgery from that of the placebo by measuring the individual painful symptoms separately.

Furthermore, we used a PRO approach by formulating reliable questions using the words, phrases and pain descriptors used by patients rather than those usually used by physicians and assessing content validity by the DELPHI method. The DELPHI method presents many advantages that enable it to deal successfully with

the heterogeneity of the description of endometriosis symptoms. Unlike other consensus methods, individuals can be included anonymously and without interacting directly with each other, which prevents the views of a minority from dominating the group [18]. The strength of the present study lies in the fact that both patients and practitioners were involved in the design of the questionnaire. It appears that doctors reject certain items when the information provided by the patients about their symptoms is not really useful for their management (non-discriminatory sign, or without prognostic value) and/or with ambiguous or erroneous meanings depending on the patient (see for example "ovarian pain"), and favor the signs that are useful for medical management of the disease. The DELPHI process, mixing different stakeholders, made it possible to select items that are easy to understand and represent the subjective experience of endometriosis, but that are also useful from a medical point of view [19].

From the methodological point of view, the fact that some statements (i. e. those involving differences in judgment between patients and practitioners) initially discarded were discussed and finally retained thus bypassing the approval criteria defined in the method section might be a deviation with the strict methodology of DELPHI. However, the modified Delphi method that we used allows for some flexibility in the process. Indeed, the method allows the experts to express themselves and to comment on the proposed items. In the present cases, these items had received favorable comments, despite the disagreement between the panel of practitioners and patients. So we decided to keep them for discussion at the physical meeting of the experts. The final decision on each item was based not only on the median score of validity and clarity, and the agreement among experts expressed as a percentage, but also on the comments of the experts and the results of the discussions between the experts [14]. The physical meeting, at the end of the two rounds of questionnaires, is very useful when it is difficult to reach a consensus or when uncertainties persist, as was the case for these items; conversely absence of a meeting may deprive the Delphi procedure of benefits related to face-to-face exchange of information, such as clarification of reasons for disagreements or discuss comments [20]. One of the main limitations of this study was the difficulty to properly assess the exact spectrum of the disease of the patients who were included in the DELPHI panel, as some of them were enrolled from a patient association. Although all these patients were diagnosed surgically, we were not able to document the location and type of the disease, which are characteristics well known to influence the symptoms [12]. Bladder endometriosis is a rare location of the disease [21], which may explain the difficulties to reach a definitive conclusion about painful urinary tract symptoms. For this reason, we took the unorthodox step of reintroducing a non-selected item in the final questionnaire. Nonetheless, it is important to note that the statements used in the DELPHI process were all taken from a previous qualitative study with a very robust control of the spectrum of the disease [7]. Moreover, the presence in the DELPHI panel of physicians that were very familiar with the spectrum of the disease is likely to have limited this risk of bias.

An obvious flaw of the present questionnaire building process lies in the fact that it does not take into account the possibility of sensitization which is a well-known phenomenon by the physician dedicated to pain. Indeed, none of physicians dedicated to pain treatment have been included in the expert panel. The pain mechanisms related to endometriosis, as in other pain conditions, likely include some degree of interrelation between endometriosis implants and the peripheral or central nervous systems [22]. Sensitization might be an important source of variability in pain experience is that patients with identical endometriotic lesions [7]. Nonetheless, the aim of the study was to built a questionnaire focused on pain symptoms that directly relate to endometriotic lesions, for example related to microbleeding and or neural invasion, and not by sensitization, which is a nonspecific mechanism of pain, and therefore unlikely to respond to specific endometriosis treatment.

Validated PRO's in endometriosis are already available including two HrQOL instruments, the SF-36 and the EHP-30. The SF-36 is a generic instrument but has been specifically validated for endometriosis [9]. The EHP-30 is a patient-generated instrument, specifically developed to measure HrQOL among endometriosis patient. A shorter and more practical version, the EHP-5 and have proven to be a simple, efficient and valid tool for evaluating quality of life in daily practice and in clinical studies evaluating treatment efficacy [23]. Contrarily to the evaluation of the quality of life, there is clearly a lack of instrument to evaluate symptoms of the disease in daily clinical practice or in research setting. Since the early 1990s, several questionnaires have been developed to investigate the symptoms of endometriosis in epidemiological studies. These questionnaires mainly explore three major domains, severe dysmenorrhea, non-menstrual pelvic pain and deep dyspareunia [11,24–28]. These questionnaires were mainly used for research purposes. It is important to note that none of them was specifically developed on the basis of qualitative description of the patients' pain experience. This may explain the fact that a limited relationship was found between pain symptoms and endometriosis in these studies [22].

In the early 2000s, our group developed a questionnaire specifically intended to evaluate endometriosis-related pain symptoms in clinical practice [12]. The list of symptoms came from a comprehensive review of the literature and from retrospective collection of data from patients' charts. Sentences were then constructed from interviews with patients with confirmed DIE. The questionnaire included items to evaluate dysmenorrhea, dyspareunia and non-menstrual pain. The intensity of each symptom was evaluated according to a 10-cm VAS. Patients also recorded whether various (urinary or gastrointestinal) symptoms occurred or increased during menses. Using this questionnaire we were able to build an efficient prediction model of DIE based solely on questioning [12]. However, the development of this earlier questionnaire was not based on a structured PRO process, unlike the current one, which includes a solid, scientific rationale on patient description and content validation, including face validity [29]. Indeed, face validity is an important property in development of PROM's because it represents the extent to which a test is subjectively viewed as covering the concept it purports to measure.

Apart from ours, another questionnaire concerning painful symptoms of endometriosis, the daily electronic Endometriosis Pain and Bleeding Diary, underwent a proper PRO process development. The items were developed based on clinician input, but the content validity was assessed by the mean of several focus groups and three iterative sets of cognitive interviews with endometriosis patients [30]. The diary covers four aspects: dysmenorrhea, chronic pelvic pain, dyspareunia, and pain interference. As in our study, participants highlighted that two distinct types of pain (intermittent and continuous) existed and were important to measure. Again as in our study, the participants in the qualitative part of the study agreed that a 0- to 10-NRS would be appropriate to rate the pain symptoms [30]. The collection of symptoms is based on a digital daily diary allowing the change of pain over time to be recorded, to avoid recall bias and to take into account the cyclicity of the symptoms [31]. However, this renders it a complex scale to use and its utility remains to be demonstrated in comparison with simple pain scales such as ours.

As endometriosis symptoms are greatly variable according to the spectrum of the disease, having a single instrument to measure the painful symptoms of endometriosis in therapeutic trials, whether medical or surgical, would help to answer the problem of the spectrum of the disease [31]. For this reason, the Biberoglu and Behrman scale [32] was regularly used as a primary endpoint in earlier RCTs [33,34]. This scale takes in combination the three main pain symptoms, dysmenorrhea, dyspareunia and non-menstrual pelvic pain, assessed directly by the physician, as well as two signs from physical examination. Although this scale is generally regarded to represent the key symptoms and impact of endometriosis, it nonetheless suffers from several major flaws and most of all is not a PRO [31]. We thus suggest that the questionnaire we have developed could be used to measure the painful symptoms of endometriosis in therapeutic trials in a comprehensive and multidimensional way, and thus include the patient's perspective.

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Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Our study involved no intervention and was thus exempt from the French statute on biomedical research (modified version of Law 2004-806, dated August 9, 2004). Ethical review board approval was given by the French "Comité d'éthique de la recherche en obstétrique et gynécologie" (CEROG). We complied with all French statutes concerning patient data, confidentiality and restrictions.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jogoh.2017.11.003.

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