World Endometriosis Research Foundation Endometriosis Phenome and biobanking harmonization project: II. Clinical and covariate phenotype data collection in endometriosis research

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A.F.V., K.V., N.R., and A.F. should be considered similar in author order. C.M.B., K.T.Z, and S.A.M. jointly directed this work.

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Objective: To harmonize the collection of nonsurgical clinical and epidemiologic data relevant to endometriosis research, allowing large-scale collaboration.
Design: An international collaboration involving 34 clinical/academic centers and three industry collaborators from 16 countries on five continents.
Setting: In 2013, two workshops followed by global consultation, bringing together 54 leaders in endometriosis research.
Patients: None.
Intervention(s): Development of a self-administered endometriosis patient questionnaire (EPQ), based on [1] systematic comparison of questionnaires from eight centers that collect data from endometriosis cases (and controls/comparison women) on a medium to large scale (publication on >100 cases); [2] literature evidence; and [3] several global consultation rounds.
Main Outcome Measure(s): *Standard recommended* and *minimum required* questionnaires to capture detailed clinical and covariate data.
Result(s): The *standard recommended* (EPHect EPQ-S) and *minimum required* (EPHect EPQ-M) questionnaires contain questions on pelvic pain, subfertility and menstrual/reproductive history, hormone/medication use, medical history, and personal information.
Conclusion(s): The EPQ captures the basic set of patient characteristics and exposures considered by the WERF EPHect Working Group to be most critical for the advancement of endometriosis research, but is also relevant to other female conditions with similar risk factors and/or symptomatology. The instruments will be reviewed based on feedback from investigators, and—after a first review after 1 year—triannually through systematic follow-up surveys. Updated versions will be made available through http://endometriosisfoundation.org/ephect. (Fertil Steril® 2014;■:■–■. ©2014 The Authors.)

Key Words: Endometriosis, EPHect EPQ, pelvic pain, questionnaire, standardization, symptoms

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It is generally accepted that endometriosis is a heterogeneous disease with respect to its natural history, disease burden, extent of inflammation, state of progression, and phenotypic presentation of lesions and symptoms. The variability of patient "types" included in endometriosis research studies is not solely determined by the surgical characterization of the (extent of) disease during laparoscopy (1). There are important nonsurgical aspects that characterize patient (sub)populations, including symptomatology (onset, duration, extent and severity of symptoms, comorbidity) and other nonsymptomatic phenotypes such as anthropometric characteristics, ethnicity, and reproductive and demographic factors. These are important to consider in any endometriosis research study, and it may be that the inclusion of different patient populations in studies, which cannot be adequately defined or recognized as they have been poorly characterized, has led to conflicting results between studies of different populations (2).

To study phenotypic variation in endometriosis successfully, studies need to include sufficient numbers of patients to allow for the detection of differences between subphenotype groups with adequate statistical power. Collaboration and pooling of individual participant data across research centers can enable much larger sample sizes, can afford subgroup analyses, and is more effective than meta-analyses (3). However, data are often not collected in a manner that allows them to be prospectively or retrospectively compared. For example, in a study attempting to retrospectively pool epidemiologic data from 53 large population-based studies of >10,000 individuals, part of the P3G collaborative network (www.p3gobservatory.org), 47% of the variables studied were impossible to match (4). Given the variation in quality and complexity of the data collected across disparate centers, data pooling may not always be feasible, which can impede scientific progress. Moreover, standardization and harmonization of phenotypic data and biologic sample collection methods are crucial to allow meaningful comparison between different patient populations and (ethnic) groups in endometriosis research, and will aid the scientific inquiry into the etiology and pathogenesis of the disease. Indeed, successful, field-altering risk-factor and subphenotype investigations among many centers have been demonstrated by large consortia across an array of health outcomes (5–11).

The mission of the World Endometriosis Research Foundation (WERF) Endometriosis Phenome and Biobanking Harmonisation Project (EPHect) is to develop a consensus

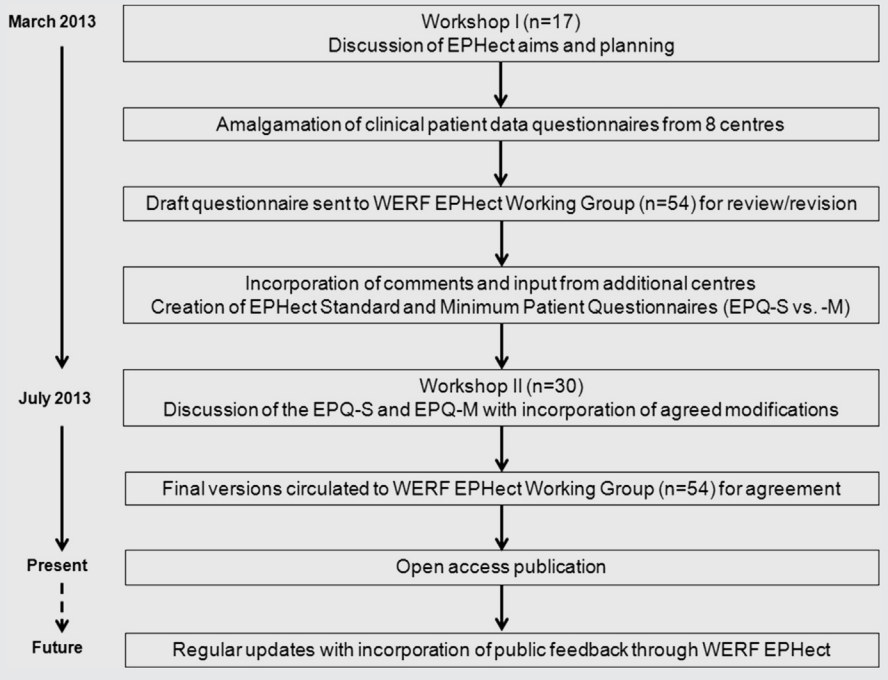
on standardization and harmonization of phenotypic surgical/clinical data and biologic sample collection methods in endometriosis research. Specifically, to facilitate large-scale internationally collaborative, longitudinal, epidemiologically robust, translational, biomarker and treatment target discovery research in endometriosis, WERF EPHect provides evidence-based guidelines on [1] detailed surgical, clinical, and epidemiologic phenotyping (phenome) data to be collected from women with and without endometriosis to allow collaborative subphenotype discovery and validation analyses; and [2] standard operating procedures (SOPs) for the collection, processing, and long-term storage of biologic samples from women with and without endometriosis. To the best of our knowledge, this harmonization initiative is unique in terms of its scope—addressing standardization of phenotypic data collection and biologic sampling protocols simultaneously for a specific disease—with a consensus reached among a large number of academic as well as industry leaders in endometriosis research. It also is a direct answer to the key priority of phenome data collection and SOP harmonization identified in Endometriosis Research Directions workshops held in 2008 (12) and 2011 (2) and will allow the investigation of a substantial number of other priorities highlighted.

In this report, we describe the development of an evidence-based, participant self-administered questionnaire for research purposes developed by the EPHect Working Group to capture nonsurgical clinical phenomic data relevant to endometriosis research. Three companion papers cover the other EPHect end points. Our previous paper in this series focused on standardization of the surgical phenome data collection in women undergoing laparoscopy (1), while two further reports will discuss the development of SOPs for acquisition, processing, and long-term storage of biologic fluid (13) and tissue (14) to enable molecular phenome investigations. We envisage that the integrated use of the EPHect phenomic data collection instruments together with the adoption of the biologic sample SOPs will for the first time allow large-scale, robust, highly collaborative research into (subtypes of) endometriosis and its associated symptoms—including elucidation of its etiology, the discovery of noninvasive biomarkers of biologically different disease entities, and the development of novel, targeted, treatments (2).

MATERIALS AND METHODS

We conducted two workshops in March 2013 and July 2013 that brought together leaders in endometriosis research worldwide to develop and reach consensus on evidence-based EPHect phenome collection and SOP guidelines, followed by several rounds of expert review by the WERF EPHect Working Group (Fig. 1). During Workshop I, four areas of standardization and harmonization were defined: [1] surgical phenotyping, [2] nonsurgical clinical/epidemiologic phenotyping, [3] and fluid sample and [4] tissue sample collection, processing, and storage protocols for molecular and genetic phenotyping. To date, the WERF EPHect global initiative has involved 34 clinical/academic centers and three industry collaborators (54 participants) from 16 countries on five continents. The WERF EPHect initiative, participants, and work flow are described in more detail in our first paper in this series on standardization of surgical phenome data collection (1).

FIGURE 1



Flow diagram depicting the WERF EPHect development and consensus process (clinical data collection).

Vitonis. Clinical data collection for endometriosis. Fertil Steril 2014.

The initial development of the nonsurgical patient questionnaire was based on questionnaire tools provided by eight centers around the globe that have collected nonsurgical information from endometriosis cases and controls on a large scale (criterion: publication on >100 cases). During Workshop I, their questionnaires were reviewed, and key topics were identified for inclusion in the EPHect endometriosis patient questionnaire (EPQ), including pelvic pain, subfertility and reproductive history, menstrual history and hormone use, medical and surgical history, medication use, and personal information. A subsequent e-mail consultation round including open invitations was sent to all 54 EPHect collaborators, asking them to review the EPHect EPQ under development and to participate in WERF EPHect Workshop II (London, 11 July 2013).

We conducted an extensive literature search in PubMed for English language publications describing associations between the key topics included in the EPHect EPQ and endometriosis. Rigorous review of the phrasing and temporality of each question on the EPhect EPQ was performed by the clinical and epidemiologic experts in the EPHect working group. Importantly, the EPHect EPQ development focused on selecting questions and rating scales that are validated in the literature, as described in this article. In addition, most questions were piloted by patients and volunteers in the centers contributing the questions, and all questions were reviewed by the workshop participants for face validity. During Workshop II, the questionnaire was presented to participants together with a summary of reviews obtained through e-mail consultation, and a consensus was obtained on the final content and format of the questionnaire (Supplemental Appendix 1, available online).

The development of the EPHect EPQ focused on information that was considered by the Working Group to be universally important to endometriosis centers in characterizing patients by their spectrum of symptoms. We did not include many potentially important exposures that may be associated with endometriosis etiologically and that may be of specific interest to some centers but were not considered crucial for patient characterization. These include, for example, nevi and freckles, sun exposure, in utero exposures, and others exposures (15). Investigators adopting the EPHect EPQ are encouraged to add any additional questions they would like to further their own scientific aims.

As described for the development of the surgical data collection instrument (1), the EPHect Working Group recognized that there are likely to be differences in resources and logistics among centers that may mean they are unable to adhere to some of the strictest standards of data collection and SOP implementation. EPHect therefore agreed on two tiers for all data collection instruments as well as for biologic sample SOPs: *standard recommended* and *minimum required*. All participants in the consultation were asked to decide which information in the EPHect EPQ should be collected as a minimum (EPQ-M) requirement and which would be recommended as standard (EPQ-S), and a consensus on this division was achieved during Workshop II.

Approval by an ethics committee or institute review board was not required for formation of the EPHect Working Group, review of existing literature, or consensus regarding best practices for endometriosis research described within the WERF EPHect four manuscript series. This endeavor did not include data from human subjects. A comprehensive list of declared conflicts of interest for each of the authors and members of the EPHect Working Group is provided.

RESULTS

Supplemental Appendix 1 provides the consensus standard EPHect endometriosis patient questionnaire (EPHect EPQ-S), with sections excluded from the minimum version (EPHect EPQ-M) highlighted. These sections focus on symptoms or characteristics pertaining across the life course. We would argue that life course data are important to characterize women with and without endometriosis, particularly in the study of endometriosis which is marked by diagnostic delay (16, 17), but these are considered of secondary importance in settings where it is anticipated that completion of the EPHect EPQ-S will impact study recruitment because of its length. However, we stress that pilot work in several EPHect centers has shown that in both paper and electronic form the full standard questionnaire requires 25 to 40 minutes to complete. We will discuss the development of each of the subsections of the EPHect EPQ-S.

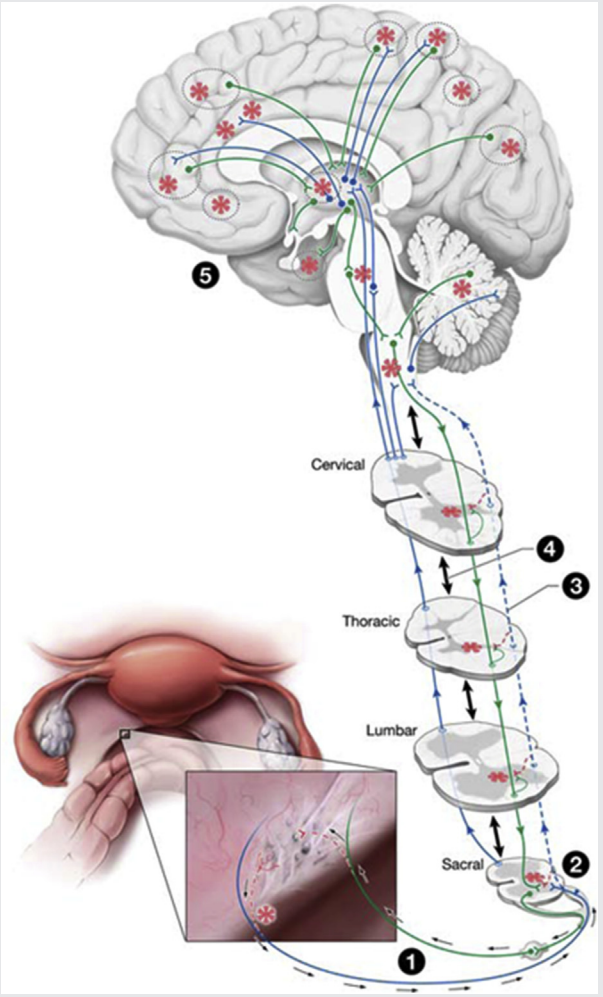
Pain

Women with endometriosis experience a variety of pain symptoms, most commonly dysmenorrhea, noncyclical pelvic pain, dyspareunia, and dyschezia. However, the relationship between endometriosis and pain symptoms is complex, with little correlation between the extent of disease seen at laparoscopy and the severity of pain experienced by the patient (18, 19). As with many other disorders that involve visceral pain, it has become apparent that there are a variety of different mechanisms by which pain could be generated in endometriosis (Fig. 2) (20), potentially producing discrete "pain phenotypes," even though our current understanding of these mechanisms is still fragmented. The pain section of the EPHect EPQ is designed to use validated measures to capture sufficient information to allow patients to be subcategorized on the basis of their pain symptoms.

The three main mechanisms generating pain are [1] nociceptive, [2] inflammatory, and [3] neuropathic or centrally generated pain, although it is likely that a combination of these processes occurs in many patients. It is plausible that these phenotypes may be characterized by different biomarker profiles or may be responsive to specific treatments only, and therefore a failure to correctly characterize the pain symptoms may obscure a significant result in such studies. Furthermore, both psychological and cognitive factors can modulate—in either a facilitatory or inhibitory manner—the pain experience, and they may also need to be considered (Fig. 3) (21).

Recommendations have been published for standard endometriosis–associated pain data collection techniques (22). Using these guidelines, the EPHect Working Group agreed that pain intensity will be measured on an 11-point numerical rating scale (NRS) anchored with 0 = no pain and 10 = worst imaginable pain. Pain affect is captured on

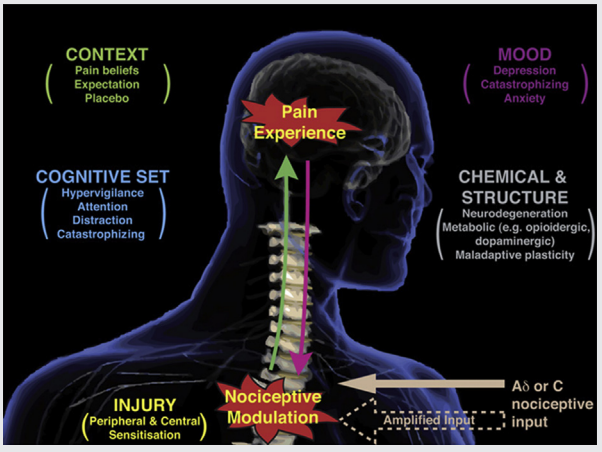
FIGURE 2



Mechanisms by which the nervous system can be engaged in endometriosis (17). Endometriotic lesions appear to be able to engage the nervous system throughout the neuroaxis. In addition to developing their own innervation [both peptidergic sensory (blue) and sympathetic nerve fibers (green)], all nerve fibers within the pelvis may become sensitized (red asterisk), as may the central nervous system. The extent of peripheral sensitization is dynamically modulated by estradiol and sympathetic-sensory coupling, and other factors may modulate central sensitization.

Vitonis. Clinical data collection for endometriosis. Fertil Steril 2014.

FIGURE 3



Factors influencing nociceptive inputs to affect pain perception (18). A variety of factors modulate incoming signals such that the experience of pain is not linearly related to the nociceptive input.

Vitonis. Clinical data collection for endometriosis. Fertil Steril 2014.

the EPHect EPQ with the short form McGill Pain Questionnaire (SF-MPQ). Though the original version of the SF-MPQ is included on the EPHect EPQ in Supplemental Appendix 1, we strongly recommend as standard the use of the most recent SF-MPQ-2, as ratings are given on an 11-point scale, similar to the measures of pain intensity, and seven additional questions allow for the calculation of four separate domains (continuous pain, intermittent pain, neuropathic pain, and affective) and a total score as opposed to the original version which only calculates two domains (sensory and affective) and a total score (23). Use of the SF-MPQ-2 requires investigators to sign a user agreement, which is why we have not reproduced it in our questionnaire.

Of all the cognitive and psychological covariates commonly measured in experimental and clinical pain studies, pain catastrophizing (24) is repeatedly identified as the one robust measure associated with indices of pain sensitivity, clinical outcomes, and behavioral expressions of pain (25). Catastrophizing is defined currently as "an exaggerated negative mental set brought to bear during actual or anticipated painful experience" (26). However, its clinical relevance is perhaps easier to understand when considering the three subscales of the measure Rumination ("I can't stop thinking about how much it hurts"), Magnification ("I worry that something serious may happen"), and Helplessness ("It's awful, and I feel that it overwhelms me"), and the older definition of a catastrophizer as "an individual who has a tendency to magnify or exaggerate the threat value or seriousness of pain sensations" (27). As the pain catastrophizing scale is valid and relevant for both patients and healthy controls (referring to any pain experienced rather than to pelvic pain specifically), acceptable to patients/controls, and comprises of only 13 questions, we consider this to be an important covariate in interpreting other pain-related information and thus have included it in the EPHect EPQ. Although pain catastrophizing is considered a trait measure (25) and thus should not be influenced by the preceding questions, we recommend as a standard data collection protocol always placing these questions before the detailed pelvic pain history as presented in the questionnaire to minimize any systematic differences across centers.

Depression, Anxiety, and Health-related Quality of Life

Collection of information on psychological state and health-related quality of life in a symptom-based questionnaire can be important as these factors may affect responses related to symptomatology and therefore may be important in patient (symptomatic) stratification. We did not include validated

measures of generic health status such as the Endometriosis Health Profile Questionnaire (EHP-30) (28) or the Short-Form Health Status Survey (SF-36) (29) because these require registration and/or payment from the individual centers. Additionally, validated depression and anxiety scales that can be helpful for patient stratification include measures such as the Beck Depression Inventory (BDI) (30) and the State Trait Anxiety Inventory (STAI) (31), both of which are also considered valid for healthy controls. Alternatively, to save time and/or space, a combined measure such as the Hospital Anxiety and Depression Scale (HADS) (32) can be used, but it has been argued that this is more useful as a measure of overall psychological distress than for accurately determining the degree of anxiety and depression (33). We recommend that individual sites consider including these additional scales (Table 1) when they adopt the EPHect EPQ.

Menstrual History and Hormone Use

Age at menarche and menstrual cycle characteristics in the last 3 months are captured in detail on the questionnaire as they [1] have been robustly associated with endometriosis (34–38), [2] are likely to influence symptom reporting, and [3] are crucial for interpretation of biologic assays. The EPHect EPQ-S includes a table on lifetime menstrual cycle characteristics while not on hormone medication, across different age ranges, which is not included in the EPHect EPQ-M. However, we highly recommend that these questions be asked as standard because early life menstrual cycle characteristics and their change over time may be important in the etiology of endometriosis.

The International Federation of Gynecology and Obstetrics (FIGO) recommendation for defining normal menstruation and menstrual cycle characteristics includes four parameters: regularity of menses, frequency of menses, and duration and heaviness of menstrual flow (39). We have followed the FIGO guidelines for capturing regularity, frequency, and duration of flow. The FIGO classification for volume of menstrual flow is heavy (>80 mL), normal (5–80 mL), and light (<5 mL), but this objective measurement of flow is beyond the scope of the EPHect EPQ. Therefore, we have classified menstrual flow as spotting, light, moderate, and heavy using a previously validated menstrual pictogram (40).

A complete history of hormone use is captured in the questionnaire, as this information is required to interpret reported symptomatology. In addition, long-term and recent hormone use can affect biomarker profiles (41–43), and it is therefore important to collect this information both to stratify subpopulations (e.g., endometriosis cases who use hormones for pain management) and to account for in biomarker research.

TABLE 1

Additional validated generic health status and depression/anxiety scales, not included in the EPHect EPQ, that should be considered by individual centers.

Generic health status
Endometriosis Health Profile Questionnaire (EHP-30)
Short-Form Health Status Survey (SF-36)
Depression and anxiety
Beck Depression Inventory (BDI)
State Trait Anxiety Inventory (STAI)
Hospital Anxiety and Depression Scale (HADS)

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Subfertility and Reproductive History

Fertility impairments such as conception delay and infertility are associated with an endometriosis diagnosis (44), though whether endometriosis precedes these outcomes as well as what the relation is between causality and diagnostic bias are unknown. In fact, subfertility and endometriosis may have a common origin, as suggested by evidence linking in-utero exposures with endometriosis. Subfertility is assessed in the EPHect EPQ by the longest time (>6 months) a study participant has tried to become pregnant without success and any tests she might have had to find the cause of the subfertility. The standard definition of infertility is 12 months of regular unprotected intercourse without achieving a clinical pregnancy (45), and this definition can be derived from data collected with the EPHect EPQ. However, as older women (such as women >35 years old) or women already known to have conditions that can lead to infertility might not try for 12 months before seeking medical intervention, 6 months was chosen as a screening cutoff. Additional questions relate to fertility advice sought, any type of infertility treatment received, and recency of this treatment. Some research aims involving infertility treatment will need additional medical record abstraction. For example, researchers focused on infertility treatment response will need to abstract data regarding ovarian stimulation protocol and response, fertilization, embryo culture, cohort characteristics, and transfer details from medical records because a self-administered questionnaire is not an appropriate method to accurately collect this information.

A detailed pregnancy history is captured in the EPHect EPQ, including age at the start of each pregnancy, type of fertility treatment used for each pregnancy, if applicable, and pregnancy outcome. Additional details for live births include whether the pregnancy was a multiple gestation, the type of delivery, and pregnancy complications. In prospective studies, increasing number of live births has been linearly associated with decreasing incidence of endometriosis (38). Retrospective studies have suggested that women with endometriosis may have higher rates of maternal complications and fetal problems such as preeclampsia and miscarriage (46–50), though these associations need further study.

Medical and Surgical History

Comorbidity is an important potential confounding factor in assessing symptom extent and severity. In the EPHect EPQ, participants are asked if they have ever been diagnosed (and at what age) with a list of ~30 medical conditions, including cancer, gynecologic diseases, pain syndromes, and autoimmune diseases, which have been (suggested to be) associated with endometriosis or its constituting symptoms in

epidemiologic studies (51–54). Any occurrence of a structural problem/birth defect of the uterus, cervix, or vagina is also ascertained and whether it was surgically repaired because of the increased incidence of endometriosis in association with such anomalies (55). Surgical history (the age at each surgery, the type of surgery, and its indication) can be etiologically related to pelvic pain symptoms and impact on symptom reporting. These data may also provide an indication of the diagnostic path women suffering from pelvic pain or subfertility have experienced. Self-reported medical history has been reported to be reliable and valid (56, 57).

Additionally, women are asked about recent bowel and urinary symptoms. To capture bowel symptoms that are common in women with endometriosis, we have included questions from the Rome III criteria irritable bowel syndrome module (58). Women with endometriosis experience bowel and urinary symptoms that are also associated with the menstrual phase (59, 60), and these are important to capture for defining case subpopulations.

A diagnostic history for endometriosis is canvassed in detail, including age at first symptoms, age and method of diagnoses, and any prior surgical treatments. A family history of endometriosis or of chronic pelvic pain is also obtained, while recognizing that accuracy of diagnosis has varied across generations.

Medication Use

Collecting information on recent medication use is important for biomarker research as some drugs may interact with the biomarkers to be studied and may thus distort the results. Although the medication use assessment in the patient questionnaire does not capture recent use in detail, our companion reports on biologic fluids and tissue collection and processing (13, 14) contain a biospecimen collection tool developed to capture medication use in the 30 days and 48 hours before specimen collection, including herbal medications. The purpose of the prescription medication and over-the-counter pain medication lists included in the EPQ is to capture medication use that could have influenced how women respond to questions or highlight patterns of use (for example, sleeping aids) that are more prevalent among women with endometriosis or with pain symptoms relative to those without. Medications for chronic pain or inflammatory conditions or for other symptoms, such as depression or anxiety, may affect pain reporting. Moreover, experimental data suggest that anti-inflammatory drugs may affect the severity of the disease (61, 62).

Personal Information

The demographic data that are required for interpretation of any epidemiologic study result include age, race/ethnicity, major ancestry, and highest level of education attained, and are collected on the EPHect EPQ. Race/ethnicity is assessed with categories previously used in a worldwide study (63). However, we realize these categories may not sufficiently capture all populations where this questionnaire will be used. Investigators using the questionnaire are permitted to alter or add categories as they see fit, but we request that any changes still allow categories to be collapsed to their current form to ensure that cross-study data harmonization will continue to be possible.

The anthropometric exposures captured are body mass index (BMI; current height and weight), most and least weighed since age 18, somatotype by age range (64), and body shape by age range (65). Current BMI has been shown to be inversely associated with endometriosis (66) and validly measured by self-reported questionnaire (67–69). Greater body size and adolescent weight have both been shown to be associated with a decreased risk of endometriosis (66, 70). Two questions on hair and eye color, previously associated with endometriosis (71–75) and possibly useful in marking genetic subpopulations, are also included.

Basic questions on three lifestyle covariates are included in the questionnaire: smoking, alcohol use, and exercise. Smoking and alcohol use, which have been associated with endometriosis in a prospective study (76), are captured as former and current smoking and packs per day as well as current number of alcoholic drinks per week. Recent physical activity is assessed as the average time spent per week during the past year on various activities, allowing for the calculation of metabolic equivalent (MET) scores. The reproducibility and validity of self-administered questionnaires on adult physical activity were examined in a prospective cohort and found to be appropriate for epidemiologic research (77).

DISCUSSION

To facilitate collaboration among endometriosis researchers that is not stymied by incompatible data collection, we encourage researchers worldwide to adopt the EPHect EPQ. The questionnaire can be completed by any woman undergoing investigation for symptoms of endometriosis (whether she has the disease or not), or asymptomatic women, subject to signed written informed consent obtained from each patient and local ethics approval for the study according to ethical principles for clinical research summarized in the Declaration of Helsinki. To enable the multicenter collaborations, envisaged by the WERF EPHect initiative, it is essential that centers adopting the WERF EPHect instruments and SOPs ensure that patients provide informed consent that allows their data and biologic samples to be used in future multicenter (inter)national collaborations, and that appropriate ethics committee and institute review board approval is obtained that allows for such collaborations. Additionally, individual sites and their institutional review boards will need to determine whether systems should be in place to flag specific responses to any question for urgent local clinical review.

The EPQ is not designed for use in clinical practice to inform immediate clinical decisions. Many physicians ask patients to complete questionnaires that they have been designed ad hoc for their clinical practices, and some may find portions of the EPQ to be of interest for that purpose. However, the questionnaire was not designed to accommodate in-clinic completion and immediate review, as this is beyond the scope and inconsistent with the goals of EPHect.

Additionally, to our knowledge, none of the longstanding, validated component parts of the EPQ have been applied in an immediate point-of-care setting. Individual physicians and their institutional review boards will need to determine what, if any, data they would like to include in the clinical record. This would be equally true for results from discovery testing conducted using the biologic samples collected in compliance with EPHect protocols.

The EPHect EPQ captures details on pain, menstrual and reproductive history, medical history, hormone use and infertility, and demographics and lifestyle characteristics and is sufficient to capture the minimum nonsurgical clinical phenome in endometriosis cases and controls. The exposures and characteristics assessed in the questionnaire were included because they have all been associated with endometriosis in published literature. Although the questionnaire is freely available, we request that researchers who use it cite it appropriately and explicitly state in publications any alterations they have made to it.

One central aim of WERF EPHect is to standardize phenotypic data collection across studies of endometriosis. This standardization will promote large-scale research using multiple data sets that are characterized using the same phenotypic definitions and will simplify interpretation of concordant or discordant results among data sets. We believe that the EPHect EPQ is the most up-to-date tool for capturing the nonsurgical clinical and epidemiologic phenome specific to endometriosis and its accompanying symptoms and strongly advise the EPQ-S be adopted where possible.

The evidence base for all EPHect data collection instruments and SOPs will be reviewed continuously upon feedback provided by investigators, and through systematic surveys and follow-up reviews after 1 year and every 3 years thereafter. Thus, investigators are strongly encouraged to provide such feedback. Updates of instruments will remain freely accessible to the research community through the EPHect website (endometriosisfoundation.org/ephect). In addition, the EPHect Working Group will develop supplemental modular questionnaires that can be added to the standard questionnaire as requested by individual investigators or as scientific evidence in new or developing areas emerges. These additional modules will be reviewed and validated by the EPHect team and approved by WERF for public dissemination through the website.

In the next phase of the EPHect initiative, WERF aims to [1] develop freely available stand-alone applications as well as web-based systems to facilitate center-restricted data entry and reduce costs and time expenditure to individual centers, and [2] amalgamate a voluntary registry of centers using EPHect data collection tools and biologic sample SOPs that would offer any investigator a transparent platform for the establishment of new collaborations. We ask that publication of results that are generated using WERF EPHect data and sample collection protocols appropriately reference the sources, including version numbers, of the instruments used.

In conclusion, the EPHect Working Group stresses that the development of the EPHect EPQ and the systems to administer it are driven by a collective pursuit of advancing our understanding of endometriosis, facilitating diagnosis and treatment development, and ultimately advancing disease prevention strategies through global cooperation (1). The EPHect EPQ is a critical and necessary data collection tool designed with the input of leaders in endometriosis research worldwide to achieve the goal of facilitating large-scale cross-center, longitudinal, epidemiologically robust, biomarker and treatment target discovery research in endometriosis. If adopted by research centers across the globe, the EPHect EPQ will aid in the design and conduction of large, multicenter, geographically diverse studies with high reliability and validity, conducted on behalf of the millions of girls and women struggling with endometriosis and its associated symptoms.

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