World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project

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World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project: V. Physical examination standards in endometriosis research

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Objective: The World Endometriosis Research Foundation established the Endometriosis Phenome and Biobanking Harmonisation Project (EPHect) to create standardized documentation tools (with common data elements) to facilitate the comparison and combination of data across different research sites and studies. In 2014, 4 data research standards were published: clinician-reported surgical data, patient-reported clinical data, and fluid and tissue biospecimen collection. Our current objective is to create an EPHect standard for the clinician-reported physical examination (EPHect-PE) for research studies.

Design: An international consortium involving 26 clinical and academic experts and patient partners from 11 countries representing 25 institutions and organizations. Two virtual workshops, followed by the development of the physical examination standards underwent multiple rounds of iterations and revisions.

Subjects: N/A

Main Outcome Measure(s): N/A

Result(s): The EPHect-PE tool provides standardized assessment of physical examination characteristics and pain phenotyping. Data elements involve examination of back and pelvic girdle; abdomen including allodynia and trigger points; vulva including provoked vestibulodynia; pelvic floor muscle tone and tenderness; tenderness on unidigital pelvic examination; presence of pelvic nodularity; uterine size and mobility; presence of adnexal masses; presence of incisional masses; speculum examination; tenderness and allodynia at an extra-pelvic site (e.g., forearm); and recording of anthropometrics.

Conclusion(s): The EPHect-PE standards will facilitate the standardized documentation of the physical examination, including the assessment and documentation of examination phenotyping of endometriosis-associated pelvic pain. (Fertil Steril® 2024;122: 304–15. ©2024 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Endometriosis, standardization, harmonization, phenotyping, physical examination, EPHect

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Endometriosis is estimated to affect 10% of reproductive-aged women (and those assigned female at birth), with diverse signs and symptoms ranging from infertility, dysmenorrhea, dyspareunia, dyschezia, dysuria, fatigue, and chronic pelvic pain (1). Pelvic endometriosis has 3 anatomic subtypes (peritoneal, deep, and ovarian endometrioma) that are captured in a proposed International Classification of Diseases-11 coding classification standard (2). Furthermore, endometriosis has been identified as an underlying factor that can give rise to chronic secondary visceral pain (3). Endometriosis-associated pain can have devastating impacts on patients due to its complex pathophysiology and heterogenous presentations, from cyclical pain to daily pain, accompanied by systemic symptoms such as fatigue, and a consequent significant impact on mental health (4). The heterogeneity of the disease with respect to its natural history, clinical presentation, and treatment response creates significant challenges when comparing research findings or conducting large-scale, multicentered research when no consensus exists regarding minimum standards for research data collection. As in other diseases, there has been a need for standardized research data collection tools in endometriosis to compare and combine data from different sites to facilitate collaborative research.

Targeting this goal, the World Endometriosis Research Foundation (WERF) established the Endometriosis Phenome and Biobanking Harmonisation Project (EPHect), a global consensus for the standardization and harmonization of endometriosis research data. In 2014, the first 4 EPHect data research tools were published for the collection of clinician-reported surgical data, patient-reported clinical data, and fluid and tissue biospecimens (5–8). Each tool consists of a "minimum" and a "standard" version, which encompass standard operating procedures for rigorous uniform data and biospecimen collection methods in endometriosis research. The tools are available open access (5–8) and also at ephect.org.

As of August 2023, 58 sites from 24 countries are conducting research adhering to the EPHect standards. The EPHect patient-reported clinical data tool has been translated with cultural adaptation into 18 languages (9–11), and implemented in different ethnic (12), geographical (13), and age (14) populations. The standards have also been used for numerous discoveries, for example, to quantify clinical symptomatology (15, 16), and associate biomarkers (17–19), genomic loci (20, 21) and epigenetics (22), mental health (23), and early life events (24) with endometriosis.

Despite these advances, there remains a gap in the rigorous, systematic, documentation of research data derived from the physical examination of patients with endometriosis. A comprehensive, standardized, physical examination can provide insight into clinically detectable endometriosis and potential pain mechanisms in patients with endometriosis (25). For example, even in patients who undergo surgery for endometriosis (and thus are surgically phenotyped), there are highly relevant findings in patients with endometriosis that cannot be assessed through surgical visualization (26). These include other pain-generating and maintaining factors (e.g., bladder, bowel, and musculoskeletal) and psychological comorbidities, which can be related to underlying peripheral and central nervous system sensitization which can be seen in those with endometriosis (27). These central nervous system mechanisms can give rise to what is now termed nociplastic pain (28–30). The physical examination can help identify these other pain generators to increase understanding of these clinical findings and, therefore, improve methods of phenotyping on the basis of factors related to pain mechanisms in combination with anatomical findings – essential to advance personalized treatment. In addition, with the move toward nonsurgical clinical diagnosis and empiric medical treatment of symptoms in patients with a working diagnosis of endometriosis (4, 26, 31, 32), systematic physical assessment and pain-focused phenotyping can enhance early clinical diagnosis and monitor signs and symptoms during follow-up. This includes clinical findings consistent with palpable disease (e.g., deep endometriosis), which can be identified and assessed without surgery via physical examination.

Therefore, there is a need to collect harmonized physical examination data to supplement the other EPHect research standards. In this article, we propose the EPHect physical examination (EPHect-PE) research data standards with common data elements, and the methods leading to their development. Resources are also provided to standardize physical examination procedures for the EPHect-PE.

METHODS

The process for establishing the WERF EPHect-PE data research tool is illustrated in Figure 1. Institutional Review Board status was not required for this article. A proposal was developed, presented to, and approved by the WERF Board. For the EPHect-PE Working Group, a core group was created representing 5 gynecologist clinician-researchers (P.J.Y., C.A., K.V., P.S., and S.A.-S.) who have published original research on the topic of the physical examination in endometriosis and endometriosis-associated pain (27, 33–38) as well as 2 representatives from WERF (L.H. and S.A.M.). A broader group within the EPHect-PE Working Group was created to include a clinical fellow who performed literature reviews (J.L.), individuals representing patient and advocacy groups (D.B., F.J., and A.T.), 2 additional WERF representatives (G.D.A. and L.R.), a physiatrist (physical medicine) clinician–researcher collaborator with one of the core group gynecologists (J.S.) (35, 36), and an international expert in pain science who has published extensively on pain assessment including nervous system sensitization testing in endometriosis and pelvic pain (L.A.-N.) (39–44). The process was coordinated by a clinical fellow (T.L.) with the support of WERF (L.H.).

The proposed scope of the EPHect-PE tool was for a standardized approach to the examination of both clinical evidence of endometriosis lesions and pain phenotyping to provide insight into the underlying pain mechanisms in each patient. As with previous EPHect tools, a "standard" version to document the complete recommended physical

examination findings was created alongside a "minimum" version with the essential core components to be used in circumstances of logistical or time constraints.

Virtual workshops were held with the core and broader group. The workshops consisted of the following activities: agreement on the goals of the workshop, a summary of the literature review results, and identification of the current knowledge gaps for physical examination in endometriosis; presentation of the state-of-the-art of pain assessment with a focus on pelvic pain and endometriosis (L.A.-N.); and sessions on the pelvic examination for endometriosis (C.A.), pelvic floor and vulvar assessment (P.J.Y.), neurologic examination including for allodynia (S.A.-S.), myofascial/musculoskeletal examination (P.S. and J.S.), and quantitative sensory testing (QST) (K.V.). The core group members also shared physical examination forms that they currently used in their clinical and research activities (e.g., on the basis of those of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain network (45)). During each session, potential items for the EPHect-PE standard were identified and discussed which involved core common data elements for a pain- and endometriosis-focused physical examination.

The initial EPHect-PE "standard" and "minimum" tool was developed, along with accompanying images and videos. The initial drafts of the EPHect-PE went through iterative rounds of feedback and revisions with the core and broader members of the EPHect-PE Working Group. Stakeholder consultation was then conducted with international pain associations and additional national patient organizations. Leadership in these organizations were contacted, who identified individuals to provide further feedback on the draft standards and were included as members of the WERF Physical Examination Working Group (see Acknowledgment section: E.A., J.C., E.C., H.G.C., A.W.H., A.J., G.L., D.C.M., O.C.N., and F.F.T.).

After the stakeholder consultations, the draft EPHect-PE tool was further revised and then approved by the core and broader group members. The accompanying manuscript was written, revised, and approved by the full EPHect-PE Working Group comprising a total of 26 clinical and academic experts and patient partners from 11 countries representing 25 institutions and organizations.

RESULTS

The EPHect-PE tool in its standard form is provided in Appendix 1 (available online) and in its minimum form in Appendix 2, with the rationale behind each examination item described below. In addition, videos and photos of the myofascial/musculoskeletal examination are available online (Appendix 3). These standards can be applied to patients with both confirmed endometriosis (e.g., previous visualizing surgery or radiologic imaging) or with suspected endometriosis (as part of a clinical diagnosis) (4), in addition to comparison or control groups (46) such as those with pelvic pain without endometriosis, chronic pain at sites other than the pelvis, endometriosis without pelvic pain, or healthy persons with no signs of symptoms of gynecologic conditions.

Patient-Reported Information (A1–A5)

Before the physical examination, it is recommended that patients complete the EPHect Endometriosis Patient Questionnaire (EPHect-EPQ) for clinical and covariate phenotype data collection, which focuses on the symptoms and characteristics of pelvic pain, fertility, menstrual and reproductive history, hormonal/pain medication use, medical history, comorbidities, and personal information across the life course of that person (6). However, in circumstances where the EPHect-EPQ was completed >3 months before the physical examination, items selected from the EPHect-EPQ merit repeating at the time of examination (see the supplementary section of the EPHect-PE in Appendices 1 and 2). These items may influence physical examination findings and also include the last menstrual period, any hormonal therapy, as well as the use of analgesics and neuromodulatory pain medications.

Before the physical examination, the patient is also asked to rate their overall pain severity and pelvic pain severity on the day of the examination on an 11-point numeric rating scale (NRS) from 0 to 10, with 0 representing no pain and 10 representing worst imaginable pain. The NRS score is then compared with the average overall or pelvic pain severity over the last 4 weeks as a reference pain level. Included in the standard physical examination assessment is the use of a body map (47–50) to allow quantification of a widespread pain index. Both forms use the Michigan Body Map (49, 50), which can be collapsed to the Fibromyalgia Body Map (47, 48), both being widely used in chronic pain clinical care and scientific discovery. The widespread pain index has confirmed clinically translational validity in associations with more opioid use and persistent pain after hysterectomy (51, 52).

A detailed explanation for the purpose and step-by-step process of the examination should be provided and consent for the physical examination should be obtained from the patient before beginning the examination. Examiners (i.e., individuals performing the examination) should have a trauma-informed approach to care and create opportunities for the patient to have input, choice, and control over components of the physical examination (53).

Anthropometrics (B1–B3)

With patient permission, the examiner measures height and weight from which body mass index can be subsequently calculated.

Reproduction of Pain

For each physical examination component, the examiner asks whether each maneuver reproduces at least some aspect of the patient's pain (25). This information aims to isolate which examined organ or structure can reproduce the pain specific to the individual being examined. For example, a patient with the primary complaint of left lower quadrant (LLQ) pain is found to have an LLQ abdominal wall trigger point and left uterosacral nodule that reproduces the LLQ pain,

suggesting both myofascial pain and deep endometriosis in the etiology of this pain.

Pelvic Girdle and Back (C1–C11)

Items C1–C9 represent tests of pelvic girdle pain (PGP), defined as pain between the upper iliac crests and gluteal folds in the region of the sacroiliac joint (54). Pelvic girdle pain is known to be important in pregnancy-associated pain but may also play a role in pelvic pain outside pregnancy. Five examination maneuvers were adapted from Tu et al. (54): long dorsal sacroiliac ligament tenderness, active straight leg raise, Faber test, posterior pelvic pain provocation test (P4), and symphysis pubis tenderness. Detailed instructions, pictures, and videos are provided in Appendix 3 to facilitate consistency in examination techniques. In addition to the PGP tests, the examiner palpates the lumbar paraspinal musculature for tenderness (L1–L5) as there can be lumbar components of both back and pelvic pain (54).

Abdomen (D1–D6)

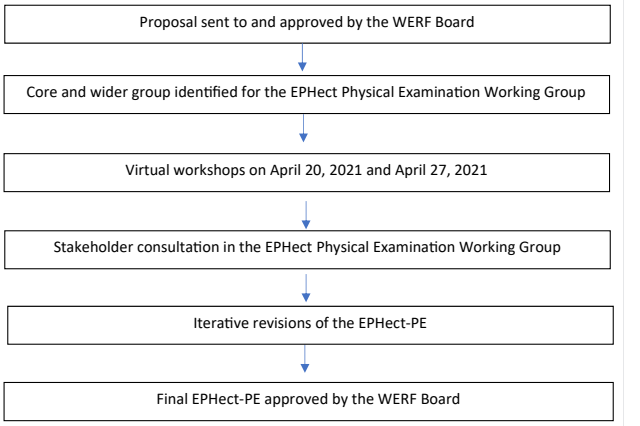
The abdomen is divided into 5 regions: left upper, right upper, left lower, right lower, and suprapubic region. Allodynia is tested by brushing a Q-tip or cotton swab from cranial to caudal on the right and left abdomen, and then from lateral to medial. Abdominal wall cutaneous allodynia has been shown to be able to discriminate between those with continuous pelvic pain, compared with those with cyclical pain or controls (55–57).

Light palpation is done in each region for tenderness and, if present, the Carnett's test is performed to differentiate the abdominal wall from visceral sources of pain (58). In this maneuver, the abdominal wall musculature is contracted, and the test is positive if tenderness remains the same or worsens, which suggests an abdominal wall source of pain (58). A positive Carnett's test was associated with greater severity of chronic pelvic pain in a cohort consisting primarily of patients with suspected or diagnosed endometriosis (27, 59). Furthermore, in each region, the examiner also palpates for myofascial trigger points, defined as "a hyperirritable spot in a taut band of a skeletal muscle that is painful on compression, stretch, overload, or contraction of the tissue which usually responds with a referred pain that is perceived distant from the spot" (60). Myofascial trigger points were associated with other signs of central sensitization in patients with endometriosis (35, 36). Similarly, all previous surgical incisions on the abdomen are examined for allodynia, tenderness, and masses. The differential diagnosis of an incisional mass includes but is not limited to a hernia, abdominal wall endometriosis, and desmoid tumors. Detailed instructions, pictures, and videos are provided in Appendix 3.

Pelvic Examination: Consent

The decision to proceed with the pelvic examination involves shared decision-making between the examiner and the patient, with the goal of having each patient believe prepared for the procedure and in control. A pelvic examination only occurs if the patient declaratively consents. If an individual does not consent to the pelvic examination, they may still choose to consent to the external (abdominal and back) examination. This discussion and consent may occur at the beginning of the consultation or after the external examination. Opportunities to review the examination and its rationale should be offered in a patient-centered approach in each case. Frequent "checking-in" during the examination is important to enable the patient to ask questions or to pause or stop the pelvic examination at any time. There are circumstances where a pelvic examination may not be appropriate, such as age, cultural sensitivities, and patient choice. Patient groups that merit particular consideration, and where a pelvic examination may be omitted, include adolescents, those with a history of trauma, and individuals with vaginismus, where a pelvic examination may not be possible or may cause significant pain or distress. In addition, certain pelvic examination components are difficult for some patients (e.g., deeper pelvic examination and speculum examination), and thus these may be omitted or modified. The consent dialogue should also include a discussion of the presence of a chaperone during the examination (61). Examiners should also follow local guidelines for consent.

FIGURE 1



Flow diagram depicting the WERF EPHect development and consensus process for physical examination standards.

Lin. WERF EPHect physical exam standards. Fertil Steril 2024.

Vulva (E1–E4)

Although a detailed vulvar examination is beyond the scope of the EPHect-PE, allodynia of the labia and Q-tip palpation of the vulvar vestibule to assess for provoked vestibulodynia are included, as it is a potential source of dyspareunia and a common comorbid condition in individuals with endometriosis-related pain (62). For consistency of assessment between examiners, the vulvar vestibule is palpated in one direction, clockwise, beginning at 12 o'clock above the distal urethra. Assessment of the anocutaneous reflex is incorporated into the standard tool only for confirmation of

an intact sacral reflex. A schematic of the vulva is provided within the tool (Fig. 2).

Pelvic Floor (F1–F15)

Pelvic floor myofascial pain syndrome, characterized by hypertonicity, tenderness with palpation, and a decreased ability of the pelvic floor muscles to contract and relax, can occur in isolation but frequently co-exists with other pelvic pain conditions including endometriosis (63). Furthermore, the presence of pelvic floor tenderness itself is associated with a greater severity of chronic pelvic pain in a cohort consisting primarily of patients with suspected or diagnosed endometriosis (27). In pelvic pain patients, quantitative sensory testing pain-pressure thresholds for the palpation of pelvic floor muscles were lower (indicative of pain with lower pressure applied) compared with controls (64), and pelvic floor tenderness was associated with a higher score on the McGill Pain Inventory (65). Pelvic floor tenderness has also been found to correlate with reduced pressure pain thresholds at the thumbnail, reflecting central sensitization (38). It should be noted that pelvic floor pain could arise outside the context of central sensitization, such as from inflammation, trauma, or sporting/physical activities, and could be the source of symptoms such as dyspareunia and dyschezia.

Given the critical importance of pelvic floor myofascial pain in the pathophysiology of pelvic pain, an efficient, selective, approach for phenotyping a pelvic floor contribution to pain in those with endometriosis is incorporated into the EPHect-PE. The standard form includes a sequential examination of pelvic floor muscles from superficial to deep, integrating components described by Gyang et al. (63) and Meister et al. (66) to assess for tenderness. The superficial muscles are palpated first: bulbospongiosus, ischiocavernosus, and transverse perineal muscles. Subsequent deeper muscles palpated are the pubococcygeus, iliococcygeus, coccygeus, and obturator internus. Palpation for bands of the deeper muscles is also done. Detailed descriptions, images, and videos are provided online (Appendix 3).

For simplicity, the minimum form only consists of the palpation of iliococcygeus, which involves the further insertion of a single digit just beyond approximately 2 cm past the introitus, and palpation on the right (8 o'clock) and left (4 o'clock) (Fig. 3) (63, 66). Moreover, in the minimum tool, tenderness of the right and left iliococcygeus is assessed as present or absent.

There are no universally accepted standards for the amount of pressure to apply during pelvic floor muscle palpation for tenderness. In the study of Meister et al. (67), examiners had an average of 0.225 kg (0.5 pounds) of pressure which is approximated by tissue depression of 5.5 mm on palpation of the mid-thigh. Tu et al. (68) used 0.4–0.6 kg/cm^2 for the pelvic floor examination. Gyang et al. (63) suggested the pressure should be <2 kg/cm^2 of pressure (i.e., the pressure to induce blanching of the nail bed), whereas Shafrir et al. (38) used approximately 2 kg/cm^2 pressure for the palpation of the abdominal wall and pelvic floor muscles (38). For EPHect-PE, we recommend using an approximate pressure similar to an indentation of the mid-thigh by 5.5 mm (67), which ensures a pressure significantly <2 kg/cm^2.

After the examination for tenderness, an examiner provides an overall assessment of the pelvic floor tone graded into 3 categories: hypertonic, normotonic, and hypotonic. A clinically useful comparison is the masseter muscle contracted (hypertonic), the masseter at rest (normotonic), and the cheek (hypotonic). The patient is then asked to contract and then relax their pelvic floor muscles. The examiner assesses global pelvic floor relaxation graded into 3 categories: full relaxation (return fully to resting state), some relaxation (partially contracted), or no relaxation (remains fully contracted).

Bladder (G1 and G2)

Anterior vaginal wall palpation (extending to the vaginal wall anterior to the cervix) by a single-digit internal pelvic examination is also included to assess visceral bladder tenderness which, in some cases, may be related to painful bladder syndrome (33). Bladder and pelvic floor tenderness have been associated with a higher score on the central sensitization inventory in those with endometriosis (69). Urethra palpation, involving transvaginal palpation closer to the introitus, is also performed in the standard tool.

Deeper Pelvic Tenderness (H1 and H2)

The deeper pelvic examination is structured on the basis of whether a uterus is present. Again, a single digit (index finger) is used, without an accompanying abdominal hand as used in the bimanual examination, since the latter may activate abdominal wall myofascial trigger points and/or cause simultaneous bladder tenderness, limiting the specificity of interpretation. For patients with a uterus, a suggested order of examination would include the cervix, right paracervical (i.e., 1–3 cm lateral to the cervix, approximating the region of the right adnexa), right uterosacral ligament, cul-de-sac (including retrocervical), left uterosacral ligament, and left paracervical (i.e., 1–3 cm lateral to the cervix, approximating the region of the left adnexa). Posthysterectomy, these anatomic regions are replaced by palpation of 3 separate locations in the vaginal vault (right, central, and left) and a Q-tip palpation of the vaginal vault for focal tenderness. Similar to the pelvic floor examination, there is no universal standard for the amount of applied pressure. However, it would be reasonable to apply the approximate pressure as noted for the pelvic floor muscles.

The presence of nodularity suggestive of deep endometriosis should be formally assessed. Most published papers on the physical examination in endometriosis focus on the accuracy of palpable nodularity in predicting deep endometriosis at the time of surgery, as reviewed recently (31, 70). In these studies, there is significant variability in its sensitivity and specificity to the location of deep endometriosis (71–76). Hudelist et al. (75) found that palpable nodularity had a sensitivity for deep disease of 50% for the uterosacral ligaments, 73%–78% for the pouch of Douglas, vagina, and rectovaginal space, 25% for the bladder, and 39% for the

rectosigmoid. Moreover, palpable nodularity by itself cannot accurately diagnose the pouch of Douglas obliteration in the absence of some assessment of mobility (77). Although tenderness of these structures is common in those with endometriosis, palpation for tenderness alone has a low specificity (high false-positive rate) for observing abnormalities at surgery, including endometriosis (78), likely because the occurrence of central sensitization can result in multiple tender sites on pelvic examination regardless of structural findings.

Bimanual Examination (I1–I3)

A bimanual examination is then performed to assess uterine size, orientation, and mobility. Enlargement of the uterus can suggest concurrent adenomyosis, fibroids, or pregnancy. Uterine size is classified as either below the symphysis or above the symphysis measured in centimeters (to avoid the language of "gestational weeks," which may cause distress for patients with infertility). Mobility (or lack thereof) can be useful in assessing deep endometriosis associated with decreased mobility or fixation. Uterine tenderness may be present in patients with adenomyosis, fibroids, and/or a clinical diagnosis of "chronic uterine pain" (79). Both adnexa are palpated during the bimanual examination for the presence of tenderness, masses, and decreased mobility, suggestive of ovarian endometriomas and/or deep endometriosis. During this evaluation, the abdominal hand may activate abdominal wall myofascial trigger points and/or bladder tenderness, and thus tenderness may not necessarily indicate uterine or ovarian tenderness.

Optional Examinations (J1–J5)

If indicated (e.g., suspicion of vaginal deep disease), a speculum examination enables direct visualization of transmural invasive deep endometriosis of the vagina or endometriosis of the cervix. Similarly, if indicated (e.g., suspicion of parametrial or rectal disease) and with patient consent, a pelvirectal examination can be done to palpate nodularity (but only documented in the standard form). Otherwise, these examination items can be omitted.

Pain during and after the Examination (K1 and K2)

This assessment is performed after completing the above components of the abdominal, back, and pelvic examination. First, the patient is asked whether there was complete, partial, or no reproduction of their pelvic pain during the physical examination. Then, the patient is asked whether new pelvic pain has developed (80).

Extra-pelvic Site (L1 and L2)

The core working group extensively discussed the utility of examining extra-pelvic sites and performing QST in clinical and research settings. However, the tools or expertise to perform QST may not be universally available and has the further issue of time limitations. Thus, comprehensive QST is not included in these recommendations, but a single extra-pelvic site (a volar aspect of the distal third of the forearm (81)) was chosen to assess allodynia and tenderness (hyperalgesia).

DISCUSSION

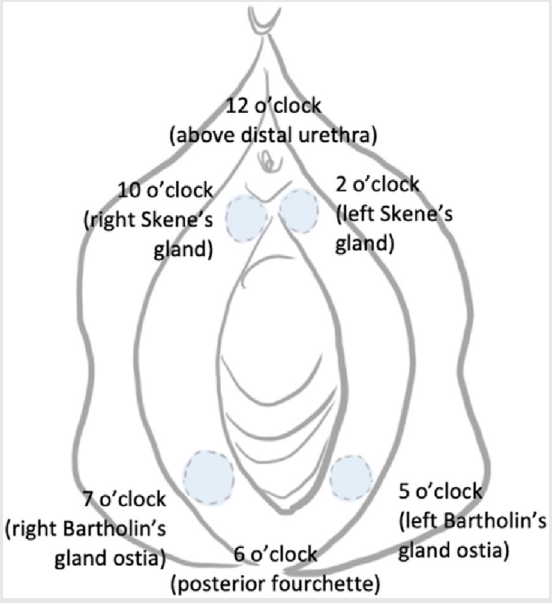
In this article, the development of physical examination data research tool of the WERF EPHect is described. Both minimum and standard forms for physical examination in research settings (WERF EPHect-PE) are provided, with common data elements consisting of patient-reported data relevant to the physical examination (e.g., last menstrual period, medication use, etc.), anthropometrics, and examination of the abdomen, vulva, pelvic floor musculature, deep pelvic region, and any relevant extra-pelvic locations. This examination encompasses physical findings related to endometriosis lesions (e.g., nodularity) and is focused on the phenotyping of pain mechanisms (e.g., features suggesting central sensitization, comorbid bladder pain, and myofascial trigger points). This phenotyping can be used alongside patient-reported outcomes of the NRS for pain and the body map for a widespread pain index, to enable diagnosis of nociplastic pain (28–30).

Because numerous professional societies increasingly support a working diagnosis of endometriosis on the basis of history and physical examination, with or without imaging, followed by initiation of empiric medical treatment of endometriosis in many clinical scenarios (4, 26, 31), this scenario may become increasingly common for research studies. The pelvic examination component of the EPHect-PE allows for the assessment of nodularity as a sign of deep endometriosis, adnexal masses that may reflect ovarian endometriomas, and uterine fixation in cases of the pouch of Douglas obliteration. As such, on the basis of physical examination, clinically diagnosed patients with endometriosis could be phenotyped into those with and without signs of deep or ovarian endometriosis. Ideally, the EPHect-PE would be combined with imaging data, whether currently published standards (82) or a future EPHect research standardized tool on imaging, to provide a relevant, noninvasive phenotype for these patients. Furthermore, biomarker data from the EPHect standards for biospecimen collection (7) could be analyzed on the basis of physical examination or imaging characteristics of endometriosis in patients with a nonsurgical diagnosis.

Although endometriosis lesion characteristics are important for nociplastic pain mechanisms, there is limited correlation between these surgical or histologic findings and pain symptoms in those with endometriosis (83). Therefore, we sought to include a physical examination assessment that potentially provides insight into other pain mechanisms, such as signs suggestive of central nervous system sensitization or involvement of the musculoskeletal system. This focus on physical examination findings alongside patient-reported symptoms such as the body map facilitates a better understanding of pain generators and the development of nociplastic pain.

Importantly, these clinical observations contribute to a better understanding of the varied etiological pathways for pain. For example, pelvic floor dysfunction could arise from trauma, inflammation due to endometriosis lesions in the

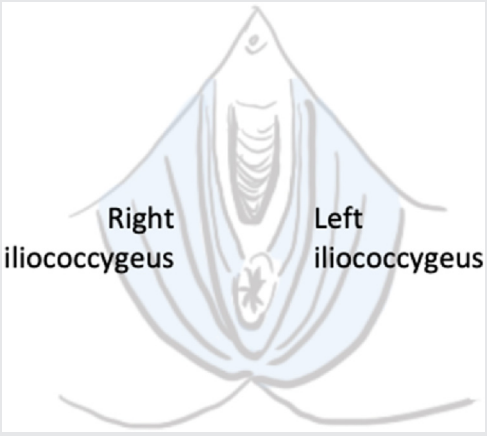
FIGURE 2



Schematic of the vulva as described in the EPHect minimum and standard forms for physical examination.

Lin. WERF EPHect physical exam standards. Fertil Steril 2024.

FIGURE 3



Examination of the iliococcygeus muscle is in both the EPHect minimum and standard forms for physical examination.

Lin. WERF EPHect physical exam standards. Fertil Steril 2024.

pelvis, or central nervous system sensitization arising from endometriosis-associated pain. Physical examination for pain phenotyping of the endometriosis patient is important to measuring pain as a clinical outcome that in and of itself must be addressed, whether surgery is performed or not. For example, a patient with endometriosis on the EPHect surgical phenotype data form (5) could have additional clinical diagnoses from the EPHect-PE, such as PGP, abdominal wall myofascial trigger points, or pelvic floor tenderness. Similarly, patients with a clinical diagnosis of endometriosis could be classified phenotypically using the EPHect-PE into those with or without provoked vestibulodynia, which would be relevant to the symptom of dyspareunia (62). These patients would be phenotypically distinct from those with endometriosis alone without other pain generators. Moreover, biomarker data from EPHect standards for biospecimen collection (8) could be analyzed on the basis of different patterns of comorbid pain generators.

The detailed instructions in this manuscript and supplementary online images/videos (Appendix 3) facilitate the consistency of the physical examination for harmonized research data collection and subsequent comparability across sites and studies. However, areas remain for further validation studies (e.g., pressure applied during palpation), and there may be inherent subtle examination differences between clinicians and within a clinician over time such as with increasing examiner experience (70). For specific studies incorporating the EPHect-PE with multiple examiners, we recommend including a process for quality assurance to better ensure consistency over the course of the study. The EPHect-PE could also be repeated over time to enable consideration of longitudinal changes in pain findings after interventions.

Notably, the EPHect-PE can be combined with patient-reported questionnaires that contribute to pain phenotyping. The Pain Catastrophizing Scale (84) is already included in the EPHect-EPQ for clinical and covariate phenotype data standards. In addition, diagnostic criteria can be incorporated on the basis of history for other chronic pain conditions, such as irritable bowel syndrome (85) and painful bladder syndrome (86, 87). Together, these assessments would enhance pain phenotyping and provide a more complete description of pain comorbidities associated with endometriosis beyond the physical examination findings. Patient heterogeneity is driven, in part, by characteristics that can only be documented by an intentional phenotypic assessment such as that described herein, without which the true biologic underpinnings of clinically translational endometriosis pain phenotypes will remain unknowable.

Strengths and Limitations

Strengths of this latest EPHect tool include the standardization of documentation of the physical examination findings and pain-focused phenotyping in individuals with endometriosis. By specifically gathering standardized clinical and patient information related to the outcome of pain, our patients with endometriosis-associated pain have the potential to be compared with other pain patient cohorts. This overarching goal has been put forth by the Innovative Medicine Intiative-National Institutes of Health Transatlantic Emphasis Group on Research and Translation-to-care Efforts for Pain consortium, a worldwide effort to advance the development of effective pain management (88). Another strength is the involvement of multiple interdisciplinary and international professionals, including patient partners and organizations for endometriosis. The engagement of patients in research is consistent with recommendations for patient-oriented, community-engaged, health research (89, 90). Patient partners

are important for developing the physical examination tool that is relevant to patient outcomes of interest; these partners guide how to consider the discussion leading to pelvic examination, the consent process, and the use of a chaperone. Additional strengths include the detailed reporting tools and visual and video descriptions. Although the EPHect tools are primarily designed for research, they may also have application in the clinical setting by standardizing the description of clinical findings and thus enhancing meaningful clinical communication about endometriosis (91).

Limitations include the inability to include recognized measures of the neurophysiologic process of central sensitization such as QST, as its inclusion requires equipment and training outside the capacity of most clinicians. Another limitation is that many physical examination components are based on expert opinion due to a limited evidence base. The physical examination standards are also predominately focused on pelvic endometriosis and are less applicable to extra-pelvic disease that is less amenable to physical examination (e.g., thoracic endometriosis). There is also a need for inter- and intra-rater reliability and reproducibility studies, and the time to complete the examination may vary on the basis of experience. Moreover, future work will determine whether patterns or aspects of physical examination findings are associated with clinically relevant outcomes (e.g., patient-reported outcomes and treatment response).

Future Directions

World Endometriosis Research Foundation will continue to document the utilization of each EPHect tool over time to evaluate the impact of these standards in enabling the comparison of studies and populations to achieve larger sample sizes pertaining to key outcomes to advance research. We see a strong need to facilitate the adoption of the pain-focused EPHect-PE in clinical drug trials for endometriosis-associated pain. The EPHect-PE could be used to phenotype study patients into subgroups, for example, based on different characteristics such as the number(s) of comorbid pain generators, reflecting the relative contribution of nociplastic pain. One might hypothesize that medical and surgical treatments that focus only on endometriosis lesions would be less effective in those patients with high nociplastic burden. Alternatively, with novel treatments, it may be possible to examine whether nociplastic pain is modifiable with effective treatment and how long it takes to observe any change. It should be noted that with future research, there may be selected items that become most important for phenotyping in endometriosis, whereas there may be other items with less utility. Similarly, subsequent studies may demonstrate that some items are overlapping in terms of the underlying factor being assessed. Therefore, there may be a refinement process of the EPHect-PE components over time.

Furthermore, additional EPHect research tools will be developed over time. As the EPHect tools are increasingly adopted worldwide, this will continue to promote collaborative studies among geographically disparate sites, maximizing the diversity of persons with endometriosis included in scientific discovery and thus clinically translational validity, ensuring sample sizes necessary for power to detect rarer but nonetheless true endometriosis-related factors, and exponentially increase our collective understanding of this complex disease.

CONCLUSION

In conclusion, we present a novel research data tool, EPHect-PE, to standardize the physical examination. This includes physical examination of signs of endometriosis lesions and the phenotyping of other pain-generating and/or maintaining factors that provide insight into potential pain mechanisms.

CRediT Authorship Contribution Statement

Tinya Lin: Writing – review & editing, Writing – original draft. **Catherine Allaire:** Writing – review & editing, Conceptualization. **Sawsan As-Sanie:** Writing – review & editing, Conceptualization. **Pamela Stratton:** Writing – review & editing, Conceptualization. **Katy Vincent:** Writing – review & editing, Conceptualization. **G. David Adamson:** Writing – review & editing, Conceptualization. **Lars Arendt-Nielsen:** Writing – review & editing. **Deborah Bush:** Writing – review & editing. **Femke Jansen:** Writing – review & editing. **Jennifer Longpre:** Writing – review & editing. **Luk Rombauts:** Writing – review & editing. **Jay Shah:** Writing – review & editing. **Abeesha Toussaint:** Writing – review & editing. **Lone Hummelshoj:** Writing – review & editing, Project administration, Conceptualization. **Stacey A. Missmer:** Writing – review & editing, Conceptualization. **Paul J. Yong:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

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Declaration of Interests

T.L. has nothing to disclose. C.A. reports consultancy fees from AbbVie and Pfizer. S.A.-S reports consultancy fees from Myovant-Pfizer, Organon, and Bayer. P.S. has received royalties from UpToDate for a section about acute pelvic pain and from *Frontiers in Reproductive Health* as Specialty Editor for Gynecology, and participated in an AbbVie advisory board and is part of a team that received botulinum toxin and funds for monitoring a clinical trial that were provided by Allergan, Inc. through a Clinical Trials Agreement with the National Institutes of Health (NIH). K.V. has received research funding from Bayer AG and honoraria for consultancy from Bayer AG, Eli Lilly, AbbVie, and Reckitts. G.D.A. reports consultancy fees from Organon, Labcorp, and Cooper, and is the CEO of and has equity in ARC Fertility. L.A.-N. has nothing to disclose. D.B. is the owner of EPP Coaching and Consulting and has received travel expenses and speaking fees from Myovant and Guerbet. F.J., J.L and L.R., have nothing to disclose. J.S. is part of a team that received botulinum toxin and funds for monitoring a clinical trial that was provided by Allergan, Inc. through a Clinical Trials Agreement with the NIH. A.T. has nothing to disclose. L.H. is remunerated by WERF as the EPHect-PE project manager. S.A.M. reports consultancy and grant funding from AbbVie for population-based research unrelated to this project and from *Frontiers in Reproductive Health* as Field Chief Editor. P.J.Y. has nothing to disclose.

The WERF EPHect Working Group (not listed in the author list): E.A. has nothing to disclose. J.C. is the IPPS vice-president and a consultant for SoLa Therapy, AbbVie, and Myovant; E.C. is an employee of Endometriosis UK; H.C.G has nothing to disclose. A.W.H.'s institution (University of Edinburgh) has received payment for consultancy and grant funding from Roche Diagnostics to assist in the early development of a possible blood diagnostic biomarker for endometriosis, consultancy fees from Gesynta and Joii, and grant funding from the UKRI, NIHR, CSO, and Wellbeing of Women for endometriosis research. A.W.H. has received payment for a lecture from Theramex, is president-elect of the World Endometriosis Society, co-editor in chief of *Reproduction and Fertility*, was a member of the NICE and ESHRE Endometriosis Guideline Groups, and is a trustee and medical advisor to Endometriosis UK; A.J. has nothing to disclose. G.L. is an employee of the US Veterans Health Administration, reports research funding from the NIH and Department of Defence, and has served as a consultant for Myovant, AbbVie, and Pelvic Sola Therapy. D.C.M. and O.C.N. have nothing to disclose. F.F.T. has royalties from Wolters Kluwer, has consulted for Bayer and Tremeau Pharmaceuticals, and received research support from Dot Laboratories.

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Proyecto de la Fundación Mundial para la investigación del fenómeno de la endometriosis y la harmonización del biobanqueo. Estándares del examen físico en investigación de endometriosis.

Objetivo: La Fundación Mundial para la Investigación en Endometriosis estableció el proyecto del fenómeno de la endometriosis y la harmonización del biobanqueo (EPHect), para crear herramientas estandarizadas de documentación (con elementos comunes de datos) para facilitar la comparación y combinación de datos entre diferentes estudios y sitios de investigación. En el 2014, se publicaron 4 estándares de datos de investigación: datos quirúrgicos reportados por los clínicos, datos clínicos reportados por las pacientes y recolección de bioespecímenes líquidos y de tejidos. Nuestro objetivo actual es crear un estándar EPHect para el examen físico reportado por el clínico (EPHect-PE) para estudios de investigación.

Diseño: Se conformó un consorcio internacional compuesto por 26 expertos clínicos y académicos y pacientes socios de 11 países representando 25 instituciones y organizaciones. Se llevaron a cabo dos talleres de trabajo virtuales, seguidos por el desarrollo de estándares para el examen físico que fueron revisados e iterados en múltiples rondas.

Sujetos: N/A

Medida(s) de desenlace principal(es): N/A

Resultado(s): La herramienta EPHect-PE provee una evaluación estandarizada de las características del examen físico y del fenotipado del dolor. Datos de la espalda y la cintura pélvica; el abdomen, incluida la alodinia y los puntos gatillo; la vulva, incluida la vestibulodinia provocada; tono y sensibilidad de los músculos del piso pélvico, sensibilidad en el examen pélvico unidigital, presencia de nodularidad pélvica, tamaño y movilidad uterina, presencia de masas anexiales; presencia de masas incisionales, examen con espéculo; sensibilidad y alodinia en un lugar extrapélvico (por ejemplo, el antebrazo), y registro de datos antropométricos.

Conclusiones: Las normas EPHect-PE facilitarán la documentación estandarizada de la exploración física, incluyendo la evaluación y documentación del fenotipo de exploración del dolor pélvico asociado a la endometriosis. (Fertil Steril 2024: Sociedad Americana de Medicina Reproductiva).

Palabras clave: Endometriosis, estandarización, armonización, fenotipificación, exploración física, EPHect.