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A modest proposal to investigate chronic uterine pain

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In female pelvic pain evaluation and management, gynecologists still lack precise methods to determine when the uterus is the primary problem. Patients with chronic pain often encounter futility seeking specific and explicit diagnostic labels for their distress. A dizzying array of supporting sources competes to advise them: the lay press, internet support sites, and all too often, cursory, balkanized initial evaluation by clinicians (ambulatory and in urgent care settings). In fact, the evidence base proving that leiomyoma-, adenomyosis-, or even endometriosis-associated uterine pain are always stable constructs over time remains distressingly small. This is particularly the case in patients with daily chronic symptoms. Hysterectomy in many cases provides a durable solution where leiomyoma, an island of adenomyosis, or a block of dense scar from a uterosacral endometriotic nodule is found in the final pathology report. Yet, there are frequent counterexamples where pain symptoms persist postoperatively despite removal of pelvic pathology. What tools might help determine when uterine surgery will be helpful? Validated clinical assessments for the presence of uterine pain on examination, and physiological studies of abnormal patterns of uterine blood flow or myometrial contractility could prove helpful, but would need systematic study in larger cohorts of women. To jump start this process, we wish to make a modest proposal – that the gynecology field deliberately define and validate a diagnostic construct known

as ***chronic uterine pain*** within the International Association for the Study of Pain's (IASP) Taxonomy of Pain umbrella term--chronic pelvic pain syndromes (CPP).[1] This philosophical reappraisal could accelerate adoption of an overarching, symptom- and exam-based approach to CPP disorders. Deliberate attention to consistent subtypes of CPP based on symptoms and location of pain, complementing histologic and imaging defined features, could refine how to select appropriate hormonal, neurological, and procedural treatments.[2] Given that only about two dozen small treatment trials for nonspecific CPP have been published and generally only have employed counseling, manual therapy, or psychoactive medications, the opportunity for progress is large.[3]

To some, adding a chronic uterine pain term may seem unproductive, leading to further splitting of a field already encumbered by excessive terminology. Yet a periodic reappraisal of terms, particularly when hypothesis driven, can be a natural, healthy development in the study of contested disease states. There is substantial justification to move to an organ-centric view of chronic pelvic pain from the successful efforts to investigate two closely related disorders, painful bladder syndrome/interstitial cystitis (PBS) and irritable bowel syndrome (IBS). Unlike endometriosis-associated pelvic pain, neither is based on histological classification, but instead are defined by organ and symptom-based diagnostic criteria. Both have benefited from extensive NIH funded multidisciplinary research portfolios, which have validated that both conditions represent mind-body integration disorders, rather than being characterized solely by peripheral inflammation. While PBS and IBS are defined by absence of visible clinical disease within the "organ of pain", investigators increasingly accept that the same central features can be present in patients with significant peripherally identifiable pathology. As a notable example, inflammatory bowel disease (IBD) is a well-recognized disorder with histological criteria for diagnosis, but it has been studied using parallel techniques for studying IBS, due to overlapping symptoms of abdominal pain. Intriguingly Keefer and colleagues have applied mind-body therapies to IBD patients and found that hypnosis in a double-blinded RCT significantly reduced IBD symptom flares over a year. They postulated this might be through immune-mediated pathways, suggesting that in turn endometriosis and other chronic uterine pain states, which also may arise from immune surveillance dysfunction, deserve similar investigation.[4]

Similarly, accumulating evidence supports the thesis that CPP patients, regardless of observable pelvic pathology, likely share common mechanisms of pain. Evidence of dysfunction in the peripheral and central nervous system can be identified broadly in women with CPP. The presence of nociceptive Aδ and C fiber nerves infiltrating endometriosis lesions was reported in both symptomatic women and rat models more than 10 years ago.[5,6] More recently, the eutopic endometrium of women afflicted with endometriosis and other causes of CPP, including adenomyosis and leiomyoma, was found to be imbued with a significantly denser nerve network than pain-free controls, suggesting that this phenomenon underlies many chronic pain states, not just those with biopsy-proven endometriosis.[7] Studies investigating markers of central pain amplification in CPP also show independence from the presence of peripheral pathology. For example, we have observed that women with CPP, regardless of endometriosis status and severity, exhibit hyperalgesia to experimental pain testing at a non-pelvic site.[8] Neuroimaging studies, which may reveal the neurobiological mechanisms of widespread hyperalgesia and altered pain sensitivity, have shown alterations in regional gray matter volume, chemistry and regional connectivity in CPP states.[9] Similar to fibromyalgia, decreased gray matter volume (GMV) in key pain regulatory regions such as the thalamus, cingulate gyrus, putamen, and insula, as well as increased concentrations of excitatory neurotransmitters in the insula, have been shown in women with CPP, again in those with and without endometriosis.[10] Furthermore, women with endometriosis without CPP did not exhibit hyperalgesia or changes in regional GMV but did demonstrate increased GMV in the periaqueductal gray (PAG), a key structure in the endogenous pain inhibitory system. This data suggests that patients with endometriosis without CPP experience little if any pelvic pain in part due to adaptive, antinociceptive activity of the CNS. Widespread hyperalgesia and parallel changes in central nervous system function is even identified in women with dysmenorrhea, prior to transitioning to chronic pain.[11] Adding a uterine-based classification for pain states would promote treatment and longitudinal studies drawn from this body of evidence, recognizing that clinical pain experience is likely determined by a complex interaction between equally important peripheral triggers (e.g., endometriosis), antinociceptive capacity (e.g. activity of the PAG), and maladaptive

changes in the CNS pain regulatory system (e.g. altered GMV, neurotransmitter levels, and connectivity).

An obvious concern may be raised with our proposal. Will use of the term chronic uterine pain discourage appropriate investigation of peripheral, intra-abdominal pathology such as endometriosis or adenomyosis? We would discourage this reductionism. Consistent description of the primary exam and symptom-based features of CPP patients in treatment trials need not interfere with current diagnostic and management strategies, while greatly encouraging prospective multidimensional analyses. We recommend continued treatment of obvious cases of extensive endometriosis or symptomatic bulky leiomyoma, but at the same time, we can conduct trials of myomectomy for smaller leiomyoma if a standardized exam repeatedly identifies uterine pain. Anecdotally, we observe that myomectomy of small < 2 cm leiomyoma does seem to help selected patients, particularly if extensive trials of hormonal suppression, physical therapy, and oral neuromodulators have already proven unsuccessful. However, at present no treatment trials exist to support this hypothesis. We could also begin aggressive tracking of putative cases of post-pelvic inflammatory disease (PID) chronic uterine pain, which based on current clinical diagnostic criteria, can only be labeled as infectious in origin. Notably, in a multi-site American randomized clinical trial of PID antibiotic treatment, utilizing clinically defined, pelvic exam-based diagnostic criteria, one-third of women still had CPP three months post-treatment. Given that no histological or culture-based confirmation was performed, at least a portion of these women may have actually been presenting with the occult onset of chronic uterine pain.[12] Likewise, IASP already defines in its Taxonomy of Pain an ovarian pain syndrome that seems largely ignored as a diagnostic entity in the published literature that would benefit from similar inquiry. A major unmet need is also to conduct a longitudinal study of the natural history of uterine pain, while also comparing trajectories between symptoms and anatomic subtypes. Published studies of the underlying pain mechanisms of women with symptomatic stage I-II endometriosis, who frequently report dysmenorrhea, are quite small because of the need to perform surgical biopsy. Freed from an endometriosis-dominant framework, studies of *chronic uterine pain* could recruit far larger cohorts. These studies still could incorporate laparoscopic findings into

subanalyses of "endometriosis confirmed" subgroups for those willing to undergo surgery.

In summary, we propose that validation of an umbrella construct, "chronic uterine pain", be subjected to stakeholder and researcher assessment, paralleling the processes used to define PBS and IBS. A working definition could start with women with pain perceived to originate from the midline deep anatomical pelvis, not clearly attributable to other nonuterine structures or obvious acute pelvic pain diagnoses. Patients should report at least 3 months of pain with pain occurring for more than 10 days per month. Focal examination of the uterus should reproduce pain consistent with the clinical symptoms during periods of pain, on 2 separate occasions at least 1 month apart with standardized transvaginal clinical palpation of the uterus. Pathologic and clinical subtypes should be captured based on imaging and prior surgical findings – leiomyoma, adenomyosis, endometriosis, and post-procedural associated pain (endometrial ablation, cesarean section, hysteroscopic tubal occlusion), with the ability to include a "not formally-assessed category" within each potential subtype.

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