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Primary Dysmenorrhea: An Urgent Mandate

Dysmenorrhea, defined as pain associated with menstruation, is subclassified as either primary, in the absence of underlying organic disease, or secondary to a specific abnormality. Potential causal abnormalities for secondary dysmenorrhea include endometriosis (and adenomyosis), uterine fibroids (myomas), congenital uterine anomalies, endometrial polyps, use of an intrauterine contraceptive device, ectopic pregnancy, pelvic adhesions, pelvic abscess, pelvic inflammatory disease, ovarian cysts, ectopic pregnancy, and, rarely, uterine or ovarian neoplasm.[1–3] Although the most common "cause" of secondary dysmenorrhea is thought to be the ectopic endometrial lesions of endometriosis/adenomyosis,[4] recent studies indicate that evidence for such causality is far from straightforward.[5] Some mechanisms and treatment of endometriosis can therefore be considered relevant to much of the discussion in this issue of *Pain: Clinical Updates*, which focuses on primary dysmenorrhea.

Primary dysmenorrhea usually begins six to 12 months after menarche and is characterized by spasmodic cramping pain in the lower abdomen that can radiate to the lower back and anterior or inner thighs. The pain usually has a clear temporal pattern: it begins a few hours before or at the start of menstruation, is most intense at onset, gradually waning over two to three days, and is sometimes accompanied by nausea, vomiting, and diarrhea, as well as headache, fatigue, nervousness, and dizziness.[3,6] Secondary dysmenorrhea, in contrast, usually begins after 25 years of age, and both the timing and intensity of pain may vary relative to menstruation; other gynecological symptoms may also be present, such as dyspareunia and menorrhagia.[2]

Primary dysmenorrhea is exceedingly common, especially in adolescents. As many as 90% of adolescent girls and more than 50% of menstruating women worldwide report suffering from it, with 10–20% of them describing their suffering as severe and distressing.

Primary dysmenorrhea is exceedingly common, especially in adolescents. As many as 90% of adolescent girls and more than 50% of menstruating women worldwide report suffering from it, with 10–20% of them describing their suffering as severe and distressing.[7–10] The pain is as intense as renal colic pain,[11] is severe enough to interfere with daily activities,[12] and can be accompanied by cardiac abnormalities.[13] Risk factors for dysmenorrhea include a positive family history, young age (<30 years), early menarche (<12 years), low or high body mass index (<20 or >30), nulliparity, smoking, longer cycles or duration of bleeding, irregular or heavy menstrual flow, premenstrual symptoms, clinically-suspected pelvic inflammatory disease, history of sexual assault, and psychological symptoms such as depression and anxiety.[14,15] Surprisingly often, dysmenorrhea, including that associated with endometriosis, co-occurs with other chronic pain conditions such as irritable bowel syndrome, low back pain, interstitial cystitis (painful bladder syndrome), chronic pelvic and abdominal musculoskeletal pain, vulvodynia, fibromyalgia, chronic headache, temporomandibular joint disease, chronic fatigue syndrome, and pain associated with ureteral calculosis.[5,16–18]

Mechanisms of Dysmenorrhea

The main mechanism thought to underlie dysmenorrhea, regardless of concurrent presence of endometriosis/adenomyosis, is uterine myometrial hypercontractility and vasoconstriction.[19–21] A growing number of factors

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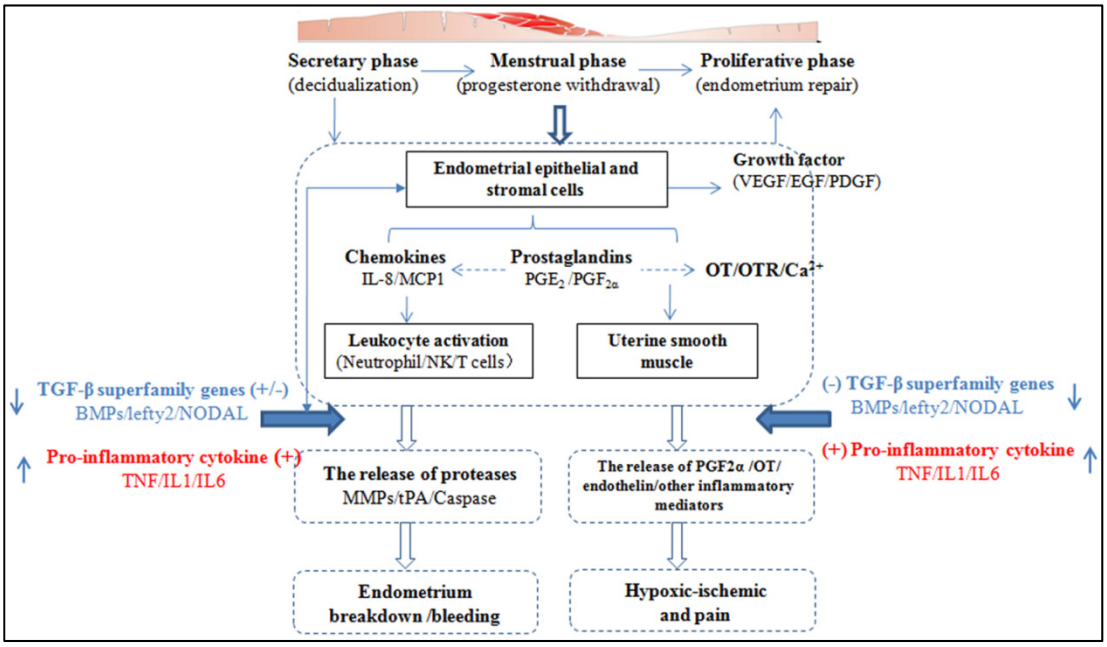

Fig. 1. A model of the biological basis of the onset of menstrual pain. Menstruation is a response to the withdrawal of progesterone and depends on complex interactions between ovarian hormones and the immune system. A variety of immune factors not only regulate the inflammation and pain in menstruation, but also affect decidualization, tissue breakdown, and early repair in the menstruation process. ↑, upregulation of gene expression regulation; ↓, downregulation of gene expression; (+), positive regulation; (–), negative regulation. Abbreviations: BMPs, bone morphogenetic proteins; EGF, epidermal growth factor; IL1, interleukin 1; IL6, interleukin 6; IL8, interleukin 8; MCP1, monocyte chemotactic protein 1; MMPs, matrix metalloproteinases; NK, neurokinin; OT, oxytocin; OTR, oxytocin receptor; PDGF, platelet-derived growth factor; PGE2, prostaglandin E2; PGF2α, prostaglandin F2α; TGF-β, transforming growth factor β; TNF, tumor necrosis factor; tPA, tissue plasminogen activator; VEGF, vascular endothelial growth factor. Reproduced from Ma et al.[22]

either within the uterus itself or in menstrual fluid or peripheral blood are proposed as contributors to these changes in uterine physiology. Such factors, some of which are shown in Fig. 1,[22] include prostaglandins, chemokines, cytokines, growth factors, oxytocin (and its receptor), leukotrienes, and vasopressin.[22–27] Another potential contributor to primary dysmenorrhea may be an increase in innervation of the endometrial and myometrial layers of the uterus, again regardless of the presence of ectopic uterine endometrial lesions, although the clinical utility of this increased innervation is currently uncertain.[5,29–31] Overall, however, little is known, even about mechanisms of uterine contractility itself,[32] to provide satisfactory hypotheses concerning how these various molecular, physiological, vascular, and potential peripheral neural factors associated with the uterus give rise to the pain[25] or even if additional contributing causes extend beyond the uterus and its environment.

Treatment of Dysmenorrhea

Given this situation, it is not surprising that systematic reviews currently confirm that only one treatment is of definite benefit for dysmenorrhea: nonsteroidal anti-inflammatory drugs (NSAIDs), which likely act by reducing uterine hypercontractility.[6,12] Unfortunately, not all women can use NSAIDs; adverse effects are not uncommon; and even in those women who are able to use them, these drugs are not universally or completely effective.[33] As shown in Table I, other likely and potentially beneficial treatments remain actively under investigation, with variable evidence on their efficacy, and even potential for harm.[1,12,34,35] Overall, therefore, a significant number of women with moderate to severe dysmenorrhea still suffer. In this context, gynecologists have come to a consensus that given that "dysmenorrhea is an extremely common and sometimes debilitating condition," best practice for treatment is "a multidisciplinary approach ... to limit the impact on daily living."[1]

Paucity of Research on Dysmenorrhea

The current limited understanding of and definitively effective treatments for primary dysmenorrhea are probably due to the fact that, despite its commonality and the resulting significant reduction in quality of life, including absenteeism from school and work,[6,36,37] this condition has received surprisingly little scientific attention. Thus, separate searches of the PubMed and ScienceDirect databases (3 June 2013), for the terms "dysmenorrhea" or "pain," showed that less than 0.1% of "pain" papers dealt with dysmenorrhea (4,936/529,651 in PubMed; 7,587/799,651 in ScienceDirect). Most of the dysmenorrhea articles, ~28%, were published in gynecological or women's health journals (ScienceDirect, 19 journals:

Table I
Current treatments for dysmenorrhea and their efficacy

Beneficial
NSAIDs (other than aspirin)
Likely to be beneficial
Acupressure
Aspirin and acetaminophen (paracetamol)
Behavioral interventions (relaxation)
Contraceptives (combined oral)
Herbal remedies (e.g., toki-shakuyaku-san)
* Hysterectomy[34]
** TENS
Topical heat (about 39°C)
Vitamin B_1 (thiamine)
Vitamin B_6[1]
Vitamin E
Unknown effectiveness
Acupuncture
Exercise[35]
Fennel[1]
Fish oil
Magnesium[1]
Magnets
Progestogens (intrauterine)
Vitamin B_{12}
Unlikely to be beneficial
Spinal manipulation
Likely to be ineffective or harmful
Surgical interruption of pelvic nerve pathways

Source: Most treatments listed are from Latthe et al.,[12] with additions from other sources as noted.

* Beneficial for dysmenorrhea; efficacy is for chronic pelvic pain.

** Transcutaneous electrical nerve stimulation at high frequency; low-frequency effects are unclear.

2,142/7,587). Astonishingly few, ~3%, were published in pain journals (ScienceDirect, 11 journals: 223/7,587), indicating that even our pain community has nearly ignored the problem.

A similar situation exists for research funding. For example, in the United States, a search of NIH Re-Porter (http://projectreporter.nih.gov/reporter.cfm) revealed that, whereas 2,938 grants are currently receiving funds in fiscal year 2013 for research that includes the word "pain," only eight grants are funded for research involving dysmenorrhea—only 0.3% of all pain research! The number of grants increases to 33 if "endometriosis pain" is added to the search, but again, the percentage is minuscule—1.1% of pain research. Other types of pain fare better. For example, 595 grants involve cancer pain (20.3%), 213 grants involve headache (7.3%), 113 grants involve fibromyalgia (3.8%), and 101 involve irritable bowel pain (3.4%). This neglect holds true even for very recent policy. In a recent publication from the Institute of Medicine of the National Academies, a distinguished panel passionately called for a complete "cultural transformation in the way pain is understood, assessed, and treated."[38] Dysmenorrhea, however, is mentioned only once, on page 33, where it is presented as an example of an acute (as opposed to a chronic) pain that "can be a recurrent problem."

Dysmenorrhea is also being ignored in current longitudinal studies designed to improve our understanding of the development of chronic pain conditions, even though dysmenorrhea is known to co-occur with them[5,16] and, importantly, even though treatment of dysmenorrhea can alleviate symptoms of the co-occurring conditions.[17] For example, in a recent study designed to assess factors that contribute to multisystem dysregulation in painful temporomandibular disorders, part of the analysis included gathering information on the patients' comorbid pain conditions.[39] The conditions considered were fibromyalgia, chronic fatigue syndrome, irritable bowel disorder, interstitial cystitis, chronic pelvic pain, frequent headaches, and frequent low back pain. In other words, although the study was confined to women, many of whom would still be menstruating (18–60 years old), dysmenorrhea (regardless of severity) was not included in the investigators' list of comorbid pain conditions. Another two examples involve low back pain, which, as stated above, is a dysmenorrheic symptom. In the first report, investigators identified the presence of headache, asthma, and atopic disease in adolescents as potential predictors of persistent low back pain in adult men and women.[40] Again, not only were data not analyzed by sex, but dysmenorrhea was not included as a potential predictor. In the second report, which describes a large longitudinal investigation now underway, and whose goal is to identify risk factors for the transition from localized low back pain to chronic widespread pain, dysmenorrhea once

again is not included as one of the possible risk factors.[41]

Why So Little Research on Dysmenorrhea?

One might reasonably ask why moderate-to-severe dysmenorrhea, which affects fully a quarter of the entire human reproductive-aged population worldwide, has been so neglected. One likely clinical factor is that dysmenorrhea's very commonality leads many adolescent and adult women to consider it a "normal" condition unnecessary to report,[8,16,41] while their clinicians, with the likely exception of gynecologists, fail to ask.[42]

This two-way failure of omission or lack of communication may be rooted in biblical and cultural attitudes toward menstruation. In many religions, menstruation is considered unclean, a time when women are to be isolated and avoided,[43,44] notably fictionalized in the novel, *The Red Tent,* by Anita Diamant.[45] A common term for menstruation is pejorative: "the curse."[46,47] For centuries, menstruation has been considered a taboo subject, famously referred to by Simone de Beauvoir in 1952 as a woman's "most intimate verity, but it is a shameful verity that she keeps hidden" (p. 619).[48] Indeed, the word "taboo" may "originate in a Polynesian word for menstruation: *tupua*" (p. 3).[46] Such attitudes continue to this day,[49,50] even in advertising.[51] Indeed, in a recent poll (July 2013) of 81 female and 50 male graduate students, ages 23–37, in the Department of Psychology at Florida State University, with a 32% response rate for both sexes, 41% of the female and 27% of the male respondents answered "yes" to the question, "Do you think that menstruation is currently a 'taboo' subject for discussion in public, advertising, etc?" (Institutional Review Board Protocol #2013.10749).

Changing Attitudes, New Findings, and a Mandate

On the other hand, and fortunately, negative attitudes toward menstruation may now be changing. Thus, in the same poll, although 36% of the students knew that menstruation had once been commonly referred to as "the curse," only one student still used the term. More importantly, regarding dysmenorrhea, in the past few years, a series of studies have been published that, viewed together, call for a change in the classification and significance of dysmenorrhea, thereby providing an urgent mandate for attention and research. The findings relate to two types of previous pain studies: brain imaging of chronic pain sufferers and the impact of pain and stress early in life on pain later in life.

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Brain Imaging

Studies of neural function during the past 20–30 years have increasingly and collectively shown that chronic pain conditions such as headache, irritable bowel syndrome, fibromyalgia, interstitial cystitis/painful bladder syndrome, temporomandibular joint disorder, osteoarthritis, and various neuropathic pains are all associated with significant, widespread, and sometimes long-lasting changes in the central nervous system's resting state, anatomy, connectivity, and chemistry.[52–54]

These findings raise an obvious question regarding dysmenorrhea. Do the brains of women with dysmenorrhea manifest similar changes? Recently, four brain-imaging studies have shown that, indeed, the brains of otherwise healthy women with moderate-to-severe dysmenorrhea compared with non-dysmenorrheic women exhibit significant differences in various aspects of their function (Fig. 2). Differences exist in cerebral metabolism (fluoro-deoxyglucose positron emission tomography)[55] and in cerebral structure (voxel-based morphometry) for both for the trait[56] of dysmenorrhea and the state of dysmenorrhea (rapid morphological changes between dysmenorrhea pain and pain-free states).[57] Differences also occur in neural activity induced by noxious skin stimulation (fMRI) in dysmenorrheic versus non-dysmenorrheic women, even when the stimulation is applied to areas remote from the pelvic/abdominal region, such as the arm.[58] This finding helps explain earlier studies showing that muscle and visceral pain sensitivity is increased in women with dysmenorrhea in both external and internal regions of the body outside the referral area for the uterus, such as the skin of the arm, the deltoid muscle, and the colon/rectum.[59–61]

Another aspect of the four brain-imaging studies is that some of the differences in neural characteristics occur throughout the cycle, i.e., chronically, even when dysmenorrheic women are not experiencing menstrual pain. These changes are consistent with recent and earlier findings that dysmenorrheic women exhibit deep muscle hyperalgesia

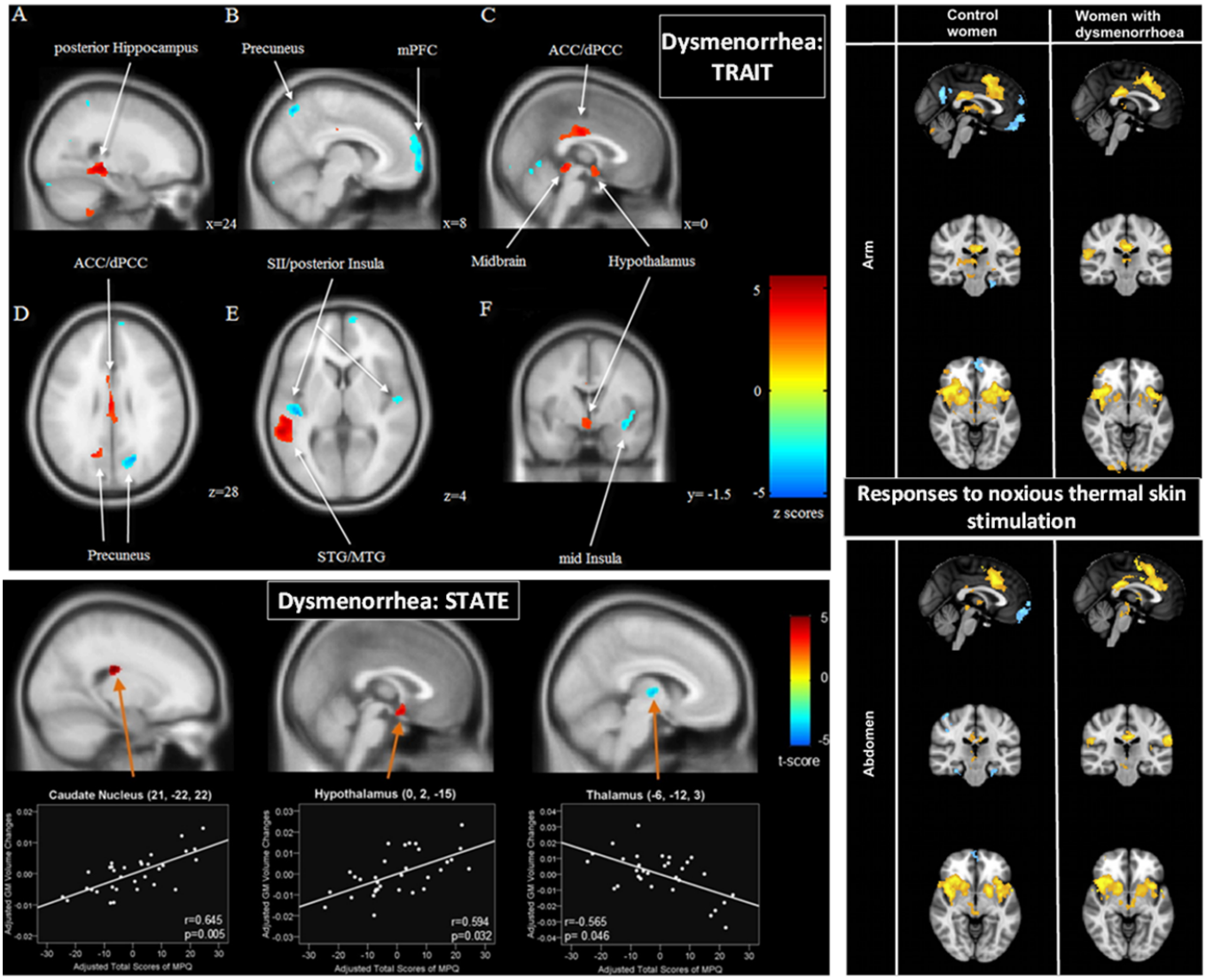

Fig. 2. Alterations in brain structure and function in women with dysmenorrhea. *Top left:* Dysmenorrhea *trait:* Significant regional gray matter (GM) volume changes in patients with primary dysmenorrhea, showing increases in the (A) right posterior hippocampus; (C) anterior/dorsal posterior cingulate cortex (ACC/dPCC, brain area [BA] 23/24), midbrain, and hypothalamus; (D) left ventral portion of precuneus (BA 31); (E) left superior/middle temporal gyrus (STG/MTG, BA 22). Decreased GM volumes were observed in the (B) right central portion of precuneus (BA 7) and medial prefrontal cortex (mPFC, BA 10); (D) right ventral portion of precuneus (BA 7/31); (E) bilateral secondary somatosensory cortex (SII)/posterior insula; (F) mid-insula. Red/blue colors represent increased/decreased volume, respectively. Reproduced with permission from Tu et al.[56] *Bottom left:* Dysmenorrhea *state*. GM volume changes correlated with current menstrual pain experience in dysmenorrhea. A positive correlation between the current menstrual pain experience and GM volume changes between phases (menstrual phase vs. periovulatory phase) was found in the right caudate nucleus and the hypothalamus, while a negative correlation was found the in left thalamus in dysmenorrhea. Red/blue colors represent positive/negative correlation, respectively. The color bar represents *t* scores. The scatterplots show the relationship between the adjusted GM volume changes at peak voxel and adjusted total pain rating index scores from the McGill Pain Questionnaire. Correlation coefficients (*r*) and corrected P values are shown. Reproduced with permission from Tu et al.[57] *Right:* Responses to noxious thermal stimulation of the skin of the left arm (top) or midline lower abdomen (bottom) in women with or without dysmenorrhea on days 1–2 of menstruation. Yellow is activation; blue is deactivation. Data shown are results of mixed-effects analyses, corrected for multiple comparisons, $z > 3$, $P < 0.05$. Reproduced with permission from Vincent et al.[58]

across their cycles.[59,62] Finally, in a fifth study, structural increases and decreases in brain gray-matter volume also occur in women with chronic pelvic pain (dysmenorrhea not assessed), regardless of accompanying endometriosis.[63]

These brain-imaging and related findings raise a new question: Is dysmenorrhea a "repetitive acute pain," as described in a recent Institute of Medicine report,[37] or do the findings justify classifying moderate-to-severe dysmenorrhea as a chronic pain condition? It has been argued that brain changes such as those observed for dysmenorrhea and other chronic pain conditions cannot be considered valid for use clinically

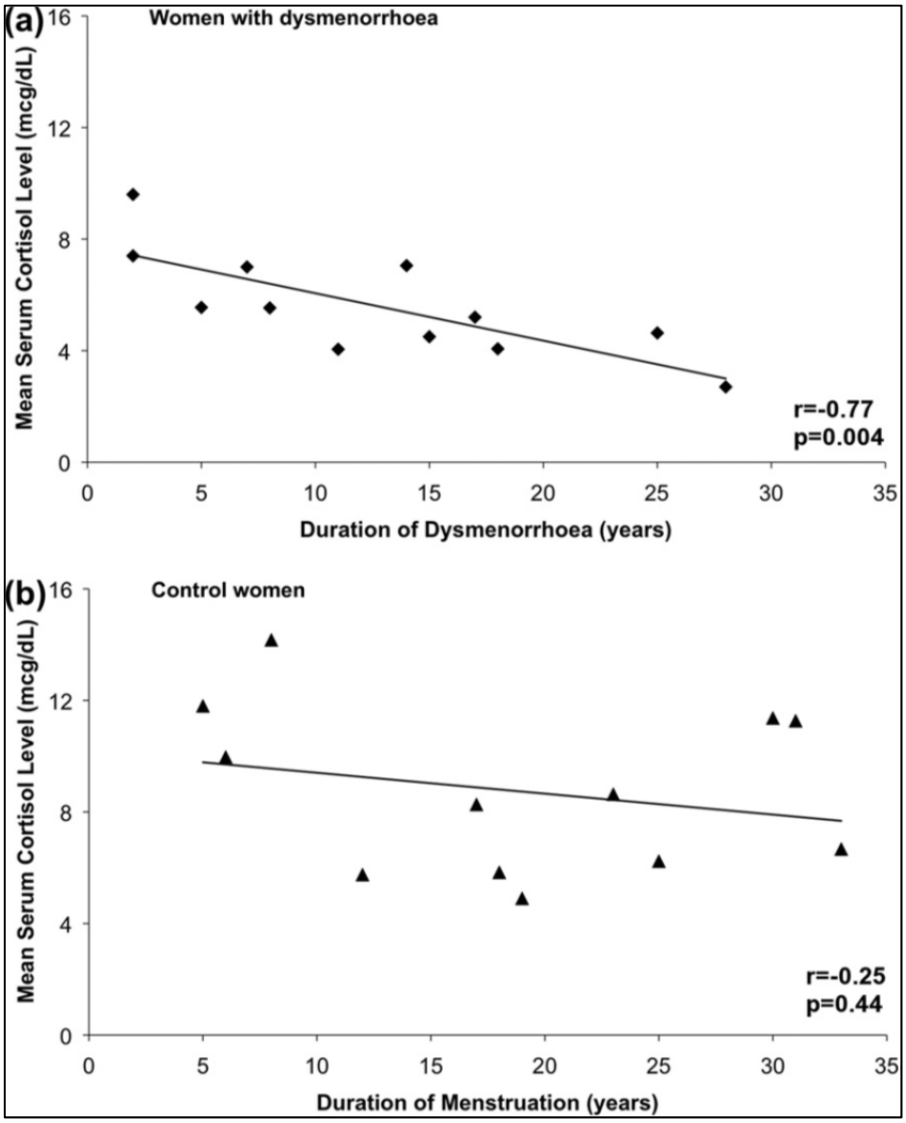

Fig. 3. The relationship between mean cortisol and duration of dysmenorrhea in (A) women with dysmenorrhea, and (B) menstruation in control women. *R*, Pearson's correlation. Adapted with permission from Vincent et al.[58]

or forensically as a diagnostic marker for chronic pain.[64,65] On the other hand, the consistency of the brain-imaging and related findings in dysmenorrheic women with those from individuals with from other chronic pain conditions nevertheless provide a strong argument that dysmenorrhea should be considered a genuine chronic pain condition.

Development of Chronic Pain

This important conclusion regarding the *clinical classification* of dysmenorrhea leads to a second area of pain research that is relevant to the *clinical significance* of dysmenorrhea—mechanisms by which chronic pain develops across the lifespan. It is generally agreed that pain and stress early in life can be a harbinger of reduced quality of life and more-severe or chronic pain later in life. Thus, epidemiological studies provide evidence that previous pain predicts future pain.[66] For example, one of the biggest risk factors for the development of chronic postsurgical pain is concurrent or previous pain.[67]

This developmental process is directly relevant to dysmenorrhea because of the large proportion of adolescent girls who suffer from severe or moderate-to-severe dysmenorrhea. Although risk factors for the development of moderate-to-severe dysmenorrhea in girls and young adults are known, I could identify no longitudinal studies concerning how dysmenorrhea in adolescent girls or young women might predispose them for the development later in life of more severe widespread pain, comorbidity with other chronic painful conditions, reduction in quality of life, psychological disorders, or pathophysiology. Only two reports were relevant. In one, Lim and colleagues found that "menstrual pain" was one of the significant risk factors for development of temporomandibular disorders over a three-year period in 266 women ages 18–34.[68] In the other, shown in Fig. 3, Vincent and colleagues made an important discovery that the longer the duration of reported dysmenorrheic symptoms (from 2 to 28 years), the greater the suppression of the woman's hypothalamic-pituitary-adrenal axis, as manifested by a reduction in cortisol.[58]

Conclusions

Primary dysmenorrhea is a condition common in women throughout adulthood that begins in adolescence, when strikingly often it is severe. Given that primary dysmenorrhea affects a quarter of the human reproductive-aged population, the paucity of studies concerning this condition is disgraceful. Our current minimal understanding of its mechanisms and limited treatment options may have been abetted by societal and clinical attitudes toward menstruation that have in the past diminished dysmenorrhea's significance. Fortunately, the concepts of menstruation as a "taboo" and a "curse" appear to be diminishing, with increasing recognition that menstrual disorders in general, particularly in adolescents, should not be ignored.[69] Indeed, recent evidence now demonstrates that dysmenorrhea is a legitimate and significant chronic pain condition, as debilitating as other well-known chronic pains, and that it can co-occur with them. Indeed, dysmenorrhea may be a fundamental factor contributing to the etiology of those other painful conditions and the associated psychological, physiological, and quality-of-life dysfunctions that are more prevalent in women.[16,57,70,71] This situation provides a strong mandate, not only for more research and clinical attention focused on dysmenorrhea, but also for its conscientious inclusion in longitudinal studies of any type of chronic pain and associated debilitating morbidity. In other words, dysmenorrhea must no longer be dismissed.[72]

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