GYNECOLOGY

Abdominal skeletal muscle activity precedes spontaneous menstrual cramping pain in primary dysmenorrhea

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BACKGROUND: Dysmenorrhea is a pervasive pain condition that affects 20—50% of reproductive-aged women. Distension of a visceral organ, such as the uterus, could elicit a visceromotor reflex, resulting in involuntary skeletal muscle activity and referred pain. Although referred abdominal pain mechanisms can contribute to visceral pain, the role of abdominal muscle activity has not yet been investigated within the context of menstrual pain.

OBJECTIVE: The goal of this study was to determine whether involuntary abdominal muscle activity precedes spontaneous episodes of menstrual cramping pain in dysmenorrheic women and whether naproxen administration affects abdominal muscle activity.

STUDY DESIGN: Abdominal electromyography activity was recorded from women with severe dysmenorrhea (n = 38) and healthy controls (n = 10) during menses. Simultaneously, pain was measured in real time using a squeeze bulb or visual analog rheostat. Ninety minutes after naproxen administration, abdominal electromyography activity and menstrual pain were reassessed. As an additional control, women were also recorded off menses, and data were analyzed in relation to random bulb squeezes. Because it is unknown whether mechanisms of menstrual cramps are different in primary or secondary dysmenorrhea/chronic pelvic pain, the relationship between medical history and abdominal muscle activity was examined. To further examine differences in nociceptive mechanisms, pressure pain thresholds were also measured to evaluate changes in widespread pain sensitivity.

RESULTS: Abdominal muscle activity related to random-bulb squeezing was rarely observed in healthy controls on menses (0.9 ± 0.6 episodes/hour) and in dysmenorrhea participants off menses (2.3 ± 0.6 episodes/hour). In dysmenorrheic participants during menses, abdominal muscle activity frequently preceded bulb squeezing indicative of menstrual cramping pain (10.8 ± 3.0 episodes/hour; $P < .004$). Whereas 45% of the women with dysmenorrhea (17 of 38) had episodes of abdominal muscle activity associated pain, only 13% (5 of 38) had episodes after naproxen ($P = .011$). Women with the abdominal muscle activity—associated pain were less likely to have a diagnosis for secondary dysmenorrhea or chronic pelvic pain (2 of 17) than women without this pain phenotype (10 of 21; $P = .034$). Similarly, women with the abdominal muscle activity—associated pain phenotype had less nonmenstrual pain days per month (0.6 ± 0.5) than women without the phenotype (12.4 ± 0.3; $P = .002$). Women with abdominal muscle activity—associated pain had pressure pain thresholds (22.4 ± 3.0 N) comparable with healthy controls (22.2 ± 3.0 N; $P = .967$). In contrast, women without abdominal muscle activity—associated pain had lower pressure pain thresholds (16.1 ± 1.9 N; $P = .039$).

CONCLUSION: Abdominal muscle activity may contribute to cramping pain in primary dysmenorrhea but is resolvable with naproxen. Dysmenorrheic patients without cramp-associated abdominal muscle activity exhibit widespread pain sensitivity (lower pressure pain thresholds) and are more likely to also have a chronic pain diagnosis, suggesting their cramps are linked to changes in central pain processes. This preliminary study suggests new tools to phenotype menstrual pain and supports the hypothesis that multiple distinct mechanisms may contribute to dysmenorrhea.

Key words: chronic pelvic pain, dysmenorrhea, nonsteroidal antiinflammatory dugs, referred pain, visceromotor reflex

Menstrual pain, also known as dysmenorrhea, affects the well-being and productivity of nearly half of reproductive-age women[1-3] and is the leading risk factor for chronic pelvic pain (CPP).[1-3] Although the hallmark symptom associated with dysmenorrhea is severe menstrual cramping, the underlying nociceptive mechanisms are not understood. Because dysmenorrhea can be resistant to available treatments, a better understanding of its mechanisms is needed to improve therapeutic strategies.[4]

Several treatments proposed to treat dysmenorrhea (including hot water bottles,[5] heat wraps,[6] microwave diathermy,[7] massage,[8] transcutaneous electrical nerve stimulation,[9] and trigger point anesthesia[10]) might plausibly target referred or primary abdominal muscle dysfunction. Despite this implied role, most prior research in dysmenorrhea has focused on prostaglandin-mediated increases in uterine contractility.[11-13]

Evidence that abdominal transcutaneous electrical nerve stimulation reduces menstrual pain but has no effect on uterine contractility[14] suggests that abdominal muscle activity may be a distinct and key contributor to menstrual pain. Such abdominal muscle activity may be due to muscle guarding or may be elicited as part of a visceromotor reflex[15] caused by visceral distension[16] because of high pressure uterine contractions.[13] Repetitive episodes of involuntary abdominal muscle activity lasting

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AJOG at a Glance

Why was this study conducted?

- To evaluate the role of referred abdominal pain mechanisms in menstrual pain by recording abdominal electromyography activity during menses.

Key Findings

- Forty-five percent of women with dysmenorrhea had abdominal muscle activity preceding a self-reported cramp.
- Such activity was rarely linked to random self-report in control participants or control days.
- Abdominal muscle activity disappeared after naproxen and was associated with primary dysmenorrhea.
- Women without abdominal muscle activity associated with cramping pain were more likely to have a secondary dysmenorrhea cause and sensory testing profiles suggestive of impaired descending modulation.

What does this add to what is already known?

- The phenotypic differences in abdominal muscle activity and sensory profiles within menstrual pain participants are consistent with the hypothesis that distinct neural pain pathways contribute to menstrual pain.

for several days could potentially elicit muscle fatigue and soreness. Despite its plausibility, there are few studies formally establishing associations between abdominal muscle activity and dysmenorrhea.

We sought to determine whether abdominal muscle activity is related to cramping pain in dysmenorrhea. To establish whether episodes of spontaneous abdominal muscle activity precede a reported cramping pain, we developed a novel method to characterize spontaneous cramping pain in real time in relation to visceromotor reflexes (VMRs).

We recorded abdominal muscle activity with electromyography (EMG) simultaneously with continuous patient self-report of abdominal cramp intensity. As a control, we evaluated the relationship between abdominal EMG activity and random event reporting in healthy controls during menses and in both groups during non-menses.

To assess mechanistic contributions, we evaluated the effects of naproxen on EMG activity and menstrual pain across a range of dysmenorrhea phenotypes. Differences between women with EMG activity related to pain (henceforth known as the VMR phenotype) and women without EMG activity related to pain (the no-VMR phenotype) were also evaluated. Because it is unknown whether mechanisms of menstrual cramps are different in primary or secondary dysmenorrhea, the relationship between medical history and EMG activity was also examined.

Finally, a common method of examining nociceptive pain mechanisms, quantitative sensory testing of pressure pain sensitivity,[17] was evaluated in women with and without the VMR phenotype. The analyses described in the previous text provide a framework for identifying specific physiological phenotypes associated with dysmenorrhea.

Materials and Methods

Participant recruitment

This study was approved by the North-Shore University HealthSystem Institutional Review Board. Following written informed consent, participants with severe dysmenorrhea and healthy controls (aged 18−45 years) were prospectively recruited from physician referral or from participation in separate studies[18] between January 2012 and February 2017. Dysmenorrhea participants were allowed to have chronic pelvic pain diagnoses, given the substantial comorbidity. These separate studies utilized magnetic resonance imaging (MRI) and/or ultrasonography alongside EMG recordings to investigate the mechanisms underlying dysmenorrhea.

Participants with dysmenorrhea were required to have menstrual pain greater than 6 on the worst day of their cycle on a numeric rating scale (NRS; 0, no pain at all, to 10, worst pain imaginable)[19] when not taking analgesic medication. The magnitude of menstrual pain was confirmed with a daily diary as described in the following text. The healthy controls were required to have menstrual pain less than 3 on an NRS without analgesic medication during menses.

Exclusion criteria for the study included a history of pelvic or abdominal malignancies, irregular menses (>45 days between menses), pregnancy within the prior 6 months, breast-feeding, active genitourinary infection in the previous 4 weeks, body mass index >40 kg/m^2, unwillingness to stop taking nonsteroidal antiinflammatory drugs (NSAIDs) on the day of the study visit, unwillingness to have a withdrawal bleed on continuous oral contraceptives, inability to read/comprehend a consent form in English, or standard MRI contraindications (because of a companion MRI study).

Between study visits, participants were asked to report their daily menstrual pain (0−10 NRS) using an online version of menstrual diaries[20] over a 1 month cycle. Participants were required to record their pain during menses for confirmation.

Study visit

Participants were scheduled for a visit during the first 48 hours following menstrual bleeding onset or during the periovulatory phase of their menstrual cycle. Participants were instructed to abstain from taking short-acting analgesic medications at least 8 hours before the visit or 12 hours for long-acting analgesics.

Upon arrival, participants were asked to rate their menstrual pain using the NRS. This reported pain served as a baseline pain that participants experienced between cramps. Dysmenorrheic participants used a 10 cm linear rheostat

attached to a visual analog scale (VAS; 0, no pain at all, to 10, worst pain imaginable) to continuously indicate their pain.

After the first 14 participants, we opted to switch our pain-recording apparatus to allow for a more rapid indication of cramping pain with a squeeze-bulb validated previously.[18] Dysmenorrheic participants were instructed to proportionally squeeze the bulb to indicate their increased pain during a menstrual cramp. Participants were instructed to squeeze the bulb only when they experienced pain above their baseline. Statistically similar results were obtained with the linear rheostat and bulb-squeeze paradigm. Therefore, we combined the linear rheostat and bulb-squeeze data for the proposed analyses.

To control for spontaneous abdominal activity, we implemented 2 control conditions. In the first control condition, dysmenorrheic participants were instructed to squeeze the bulb randomly for approximately 30 seconds every 2−5 minutes during their luteal phase. Similarly, in the second control condition, healthy controls, who do not report painful menstrual cramps, were also instructed to randomly squeeze the bulb at both visits.

To measure abdominal muscle activity, an array of 3 standard EMG electrodes was placed between the umbilicus and pubic bone of each participant. Two electrodes were placed approximately 4−6 cm laterally and 2 cm above the umbilicus. The third electrode was placed 4 cm below one of the above electrodes. EMG activity was amplified by 10,000 with an AC BIOPAC amplifier (Biopac Systems, Aero Camino Goleta, CA) and filtered between 100 and 250 Hz to isolate abdominal muscle activity. We obtained approximately 15 minutes of abdominal EMG activity from each participant.

Following baseline assessment, participants ingested 2 tablets of naproxen sodium (440 mg) and water. During a subsequent 90 minute wait time, participants filled out questionnaires to obtain complete medical, surgical, psychological, gynecological, and obstetrical history. We verified that participants reporting a history of endometriosis had reported prior surgical confirmation in their medical records.

Among these questionnaires, participants were asked to rate their typical level of menstrual pain with and without painkillers on a 100 mm VAS using an iPad. After 90 minutes, abdominal EMG recordings were repeated again for 15 minutes with bulb squeezes proportional to their new current baseline pain. At the end of the visit, participants rated their menstrual pain with an NRS.

Pressure pain thresholds

In the last 30 participants (dysmenorrhea: n = 21; healthy control: n = 9), pressure pain thresholds were obtained to establish whether deep muscle sensitivity, a potential marker of central sensitization,[21] differentiated VMR phenotypes. Pressure pain thresholds in a subset of sites historically used to evaluate chronic widespread pain/fibromyalgia[22] were obtained by a research nurse on both the menses and nonmenses visit at the right trapezius (shoulder), the right medial knee fat pad (knee), the right greater trochanter (hip), and the forehead.

A digital algometer with a 1 cm^2 rubber tip was used to measure pressure pain thresholds at a rate of between 4 and 10 Newtons/cm^2 per second. Participants pressed a button to terminate the trial when the stimulus first became painful. For safety, if the participant had not yet pressed the button by the time the examiner reached 70 Newtons, the test was terminated. A lower threshold of 40 Newtons was used for the forehead. Averaged thresholds from 2 trials with a 2 minute intertrial interval were calculated for the final analysis.

Abdominal muscle activity analysis

Participant BIOPAC files containing bulb-squeeze and EMG data were coded to blind 2 independent reviewers to both the participant group and experiment. Because abdominal muscle activity during a bulb squeeze could reflect movement artifact because of pain, we primarily examined EMG activity immediately prior to pain report via the squeeze bulb.

Abdominal EMG activity preceded pain report by about 2 seconds in our initial participants. Therefore, a window of 3 seconds was used to allow for a variable short delay in reaction time. In this study, a VMR was defined as abdominal EMG activity preceding pain report by 3 seconds. There was an 81% agreement rate on abdominal muscle activity scores between the 2 blinded reviewers for the baseline data. Because similar results were obtained with both reviewers, only results from the reviewer that analyzed both the menses and nonmenses data are presented.

Statistical analyses

In a pilot study with participants with dysmenorrhea (n = 12), we observed VMR activity in 50% of the participants with an average frequency of 10 events per hour. A power analysis using G-Power[23] for a within-subject ANOVA ($\alpha = 0.05$, 1-$\beta = 0.8$) indicated that a sample size of 34 would be needed to detect a medium effect size (dz = 0.5) reduction in VMR activity either after naproxen or on a nonmenstrual visit. Also, we predicted VMR activity would be observed less frequently (<15%) after naproxen or off menses. A power analysis for a Fisher exact test suggested a sample size of 32 would be required to identify proportional group differences after naproxen or off menses ($\alpha = 0.05$, 1-$\beta = 0.8$).

Additional dysmenorrhea participants were enrolled to accommodate technical problems or dropouts, and 10 healthy controls were enrolled for reference comparisons. Of 86 participants screened by phone, 36 were ineligible, 1 was disqualified, and 1 was lost to follow-up. Complete EMG data were obtained from all 48 participants on menses. Nonmenses data were obtained on 17 women with dysmenorrhea and 8 healthy controls. The remainder was unavailable because of scheduling limitations or loss to follow-up.

Data were analyzed in Microsoft Excel (version 2016, Redmond, VA) or Stata (version 13.1, College Station, TX), and $P < .05$ was considered the threshold for significance. A Fisher exact test was used to compare differences in proportions across the groups. A Student t test was used to compare continuous

variables such as age, self-reported NRS scores, and abdominal muscle activity frequency across the groups.

Results

Enrolled participants with dysmenorrhea and healthy controls were of comparable age and race/ethnicity (Table 1). According to daily diary entries, average menstrual pain in the dysmenorrhea cohort was 5.3 ± 0.4 on 0−10 NRS. Participants with dysmenorrhea missed 2.2 ± 0.4 days of school or work over the past 3 months. Thirty-two percent of the dysmenorrhea cohort (12 of 38) had been previously or currently diagnosed with a CPP condition (ie, bladder pain syndrome, irritable bowel syndrome) or a secondary cause of dysmenorrhea (endometriosis, leiomyoma).

To examine whether putative VMRs are related to cramping pain, we examined the relationship between abdominal EMG activity and bulb squeezing in healthy controls and dysmenorrhea participants (Table 2). An example of abdominal muscle activity preceding cramping pain is shown in the Figure.

Abdominal EMG activity related to random bulb squeezing in healthy controls on menses was rarely observed (0.9 ± 0.6 episodes/hour). Similarly, during nonmenses visits, EMG activity was rarely associated with random bulb squeezing in participants with dysmenorrhea (2.3 ± 0.6 episode/hour). In contrast, EMG activity preceded episodes of cramping pain on average 10.8 ± 3.0 times per hour in dysmenorrhea participants on their menses. Thus, the frequency of EMG activity preceding bulb squeezing in dysmenorrhea participants on their menses was significantly higher than that observed on their nonmenses visit ($P = .004$) or among healthy controls on their menses visit ($P = .001$). Putative VMRs preceding pain were detected in women with dysmenorrhea in similar proportions with use of the rheostat (50%; 7 of 14) and squeeze bulb (42%; 10 of 24; $P = .740$).

Before naproxen administration, dysmenorrheic women rated their menstrual pain 5.8 ± 0.4 on an NRS. After naproxen administration, pain was reduced to 3.4 ± 0.4 ($P < .001$). The frequency of putative VMRs was also reduced after naproxen (2.5 ± 1.1 episodes/hour) compared with before naproxen (10.8 ± 3.0 episodes/hour; $P = .001$). Whereas 45% of women with dysmenorrhea had putative VMRs (17 of 38), only 13% (5 of 38) had associated activity after naproxen ($P = .011$).

Because only a subset of women with dysmenorrhea had putative VMRs associated with cramping pain (45%; 17 of 38), we performed additional subgroup analyses to identify differences in nociceptive mechanisms (Table 3). There were no differences in age or pregnancy history between phenotypic groups (*P*'s> .4). Menstrual pain in both groups was similar on the testing day before and after naproxen (*P*'s> .3). However, participants with the putative VMR phenotype reported greater average menstrual pain without NSAIDs during a typical cycle (82 ± 2) than participants without VMR phenotype (68 ± 5; $P = .039$) on a 0−100 VAS.

Also, VMR phenotype participants reported more effective analgesia with NSAIDs (−50 ± 5) than those without (−22 ± 5; $P = .01$). VMR phenotype participants were less likely to have a secondary dysmenorrhea or chronic pain diagnosis (12% [2 of 17] vs. 48% [10 of 21]; $P = .034$). The VMR

TABLE 1
Participant demographics and self-reported pain scores

Variables	Dysmenorrhea	Healthy controls	*P* value
n	38	10	
Age	29 ± 2	26 ± 3	.479
Race/ethnicity			.169
White	29 (76.3%)	6 (60.0%)	
African-American	6 (15.8%)	1 (10.0%)	
Other	3 (7.89%)	3 (30.0%)	
Chronic pelvic pain/secondary dysmenorrhea	12 (31.6%)	n/a	n/a
Menstrual pain diary (NRS)	5.3 ± 0.4	0.8 ± 0.9	< .001[a]
Absenteeism (days/past 3 mos)	2.2 ± 0.4	0 ± 0	< .001[a]
Using oral contraceptives	7 (18.4%)	4 (40.0%)	.264

NRS, numeric rating scale; *n/a*, not available.

[a] $P < .05$.

Oladosu et al. Evaluating abdominal muscle activity in dysmenorrhea. Am J Obstet Gynecol 2018.

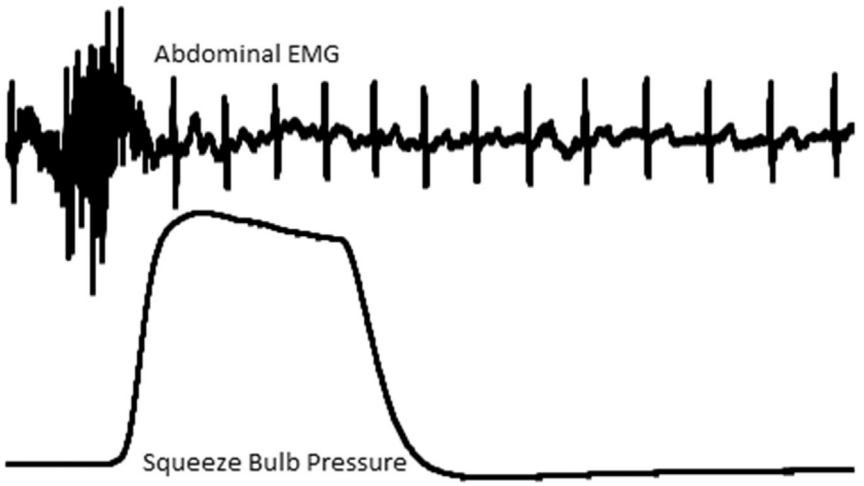
TABLE 2
Abdominal EMG patterns in women with dysmenorrhea and healthy controls

Variables	Dysmenorrhea	Healthy controls	*P* value
Nonmenses VMR/h	2.3 ± 0.6	1.0 ± 0.6	.065
Menses VMR/h			
Before naproxen	10.8 ± 3.0	0.9 ± 0.6	.001[a]
After naproxen	2.5 ±1.1	1.7 ± 1.2	.617
Before vs after naproxen, *P* value	.001[a]	.524	
Nonmenses vs menses, *P* value	.004[a]	.556	

[a] $P < .05$.

Oladosu et al. Evaluating abdominal muscle activity in dysmenorrhea. Am J Obstet Gynecol 2018.

FIGURE
Example of a VMR: abdominal muscle activity preceding menstrual cramp



The figure depicts a 10 second epoch of EMG and squeeze bulb pressure recordings. A burst of abdominal muscle activity is seen immediately preceding the bulb squeeze. The repetitive background spiking activity is EKG artifact.

EKG, electrocardiography; *EMG*, electromyography; *VMR*, visceromotor reflex

Oladosu et al. Evaluating abdominal muscle activity in dysmenorrhea. Am J Obstet Gynecol 2018.

phenotype cohort also had fewer days per month of nonmenstrual pelvic pain (0.6 ± 0.5 vs 12.4 ± 0.5; $P = .002$).

To establish whether widespread pain sensitivity differed between the groups, we examined pressure pain thresholds (PPTs). Women with putative VMRs had PPTs (22.4 ± 3.0 N) comparable with healthy controls (22.2 ± 3.0 N; $P = .967$). In contrast, women without putative VMRs had lower PPTs (16.1 ± 1.9 N) compared with women with VMRs and healthy controls ($P = .039$). There was no significant effect of day ($P = .917$) or PPT location ($P = .293$), suggesting a generalized mechanism of widespread pain sensitivity is engaged in dysmenorrheic women without VMRs.

As a final post hoc analysis, we examined the differential effects associated with CPP/secondary dysmenorrhea in women without the VMR phenotype on pain pressure thresholds. Both women with (17.1 ± 3.7 N) and without CPP/secondary dysmenorrhea (15.4 ± 1.5 N) within the no-VMR phenotype had comparably low PPTs ($P = .694$).

Comment

In this preliminary study, we sought to examine the relationship between abdominal muscle activity and menstrual pain. Women with primary dysmenorrhea often had abdominal muscle activity preceding cramping pain, more than expected by chance as demonstrated during control conditions. In contrast, women with CPP or secondary dysmenorrhea diagnoses were less likely to have abdominal muscle activity preceding cramping pain and responded poorly to naproxen. Overall, these findings suggest abdominal muscle activity contributes to certain forms of menstrual pain, which in part are characterized by the presence of a putative VMR.

This is the first report that provides evidence linking distinct abdominal muscle activity to reported spontaneous cramps in dysmenorrhea. Key strengths include the use of a novel method to record spontaneous pain, the evaluation of the experimental effects of naproxen, the implementation of control measurements (in healthy controls and on nonmenses days), and blinded analyses by 2 independent reviewers. The interrater agreement (81%) was limited because of difficulties in consistently establishing whether abdominal muscle activity was electrical artifact because of movement. However, the agreement was sufficiently high to imply that the results should be reproducible by future reviewers.

A potential bias is our choice of time interval (0−3 seconds) for temporal precedence of abdominal muscle activity before pain onset. However, this preselected time interval could reflect a 2 second delay for C-fiber−mediated conduction of pain and 1 second delay for reaction time.[24] Additionally, the cross-sectional design of this study lacks reliability analyses and prospective surgical confirmation of secondary dysmenorrhea. Although significant differences were observed between participants with dysmenorrhea on and off menses or healthy controls, findings still should be corroborated in larger studies.

We hypothesize that abdominal muscle activity preceding cramping pain is evidence of visceromotor reflexes (VMRs). As first described by MacKenzie,[15] VMRs are skeletal muscle reflexes triggered by visceral stimulation that can be sources of referred pain. VMRs have been recorded in response to colorectal,[25] bladder,[26] and uterine cervical distention[27] but not in response to uterine distension.

During dysmenorrhea, high-pressure uterine contractions occur[14] and could elicit VMRs. Although VMRs are often considered a metric for evaluating nociceptive reflexes,[28] the consistent observation of abdominal EMG activity preceding cramping pain suggests that VMRs could also be a source of referred pain during dysmenorrhea. We labeled these EMG events as putative VMRs because we did not simultaneously record uterine contractility; simultaneous uterine recordings could have interfered with electrical recordings. However, we have shown that myometrial events often precede spontaneous pain report with MRI.[18] Although direct evidence that abdominal muscle activity causes pain is lacking, an observational study evaluating the effects of lidocaine injections into abdominal muscle trigger points in dysmenorrhea supports this role.[10]

Although prior studies have not specifically been designed to identify VMRs

in humans, their results are supportive of our presented findings. The noxious perception of human colorectal distension has been associated with alterations in abdominal tension (as studied with a bellows device) along with reflexive changes in sympathetic drive.[16] Although abdominal EMG activity occurs after episodes of uterine activity during labor,[29] it is difficult to resolve which episodes of EMG activity are due to voluntary contraction.

Abdominal EMG activity may also be due to muscle guarding in anticipation of an upcoming uterine cramp.[30] Other studies investigating patients with bloating pain[31,32] identified alterations in EMG activity. A key difference between prior studies and ours is we studied the temporal association of spontaneous episodes of pain and EMG activity. Thus, in regard to our findings, studies of spontaneous pain should be performed in other pain conditions and in treatment studies to confirm whether abdominal muscle activity contributes to referred pain.

Our results also suggest different mechanisms contribute to dysmenorrhea. Symptomatic women without putative VMRs had lower PPTs and more pain throughout the menstrual cycle. The 25% reduction of PPTs in women without putative VMRs is comparable with the reduction in pain thresholds reported with chronic widespread pain in fibromyalgia.[22] Because fibromyalgia pain is associated with central sensitization and impaired descending modulation,[33] we hypothesize that alterations in central nervous system sensory processing contribute similarly to menstrual pain lacking the VMR phenotype. Notably, treating dysmenorrhea via hormonal methods or ablating endometriotic lesions has been shown to reduce symptoms of chronic widespread pain indicative of central sensitization.[21]

The phenotyping methods described here provide a novel strategy for characterizing nociceptive mechanisms in cyclical uterine pain and may ultimately predict treatment responsiveness. Our results support the idea that different subphenotypes of dysmenorrhea exist in addition to the typical differentiation of primary/secondary dysmenorrhea. Further clarification of the central nervous mechanisms contributing to menstrual pain, possibly using functional MRI of the spinal cord,[34] particularly in treatment-refractory women, would be valuable for the development of targeted therapeutics. ■

TABLE 3
Differences between participants with and without putative VMRs associated with cramping pain

Variables	Healthy	VMR	No VMR	*P* value
n	10	17	21	
Age	26 ± 3	28 ± 2	30 ± 2	.422
Prior pregnancies	3 (30%)	2 (12%)	2 (10%)	.999
Using oral contraceptives	4 (40%)	3 (18%)	4 (19%)	.999
Pain during EMG recording (NRS)				
Pain before naproxen	0 ± 0	6.0 ± 0.6	5.5 ± 0.6	.628
Pain after naproxen	0 ± 0	3.0 ± 0.6	3.7 ± 0.6	.368
Effect of naproxen	0 ± 0	−3.0 ± 0.6	−1.8 ± 0.5	.164
Self-reported menstrual pain (VAS)				
Average pain before NSAIDs	9 ± 2	82 ± 2	68 ± 5	.039
Average pain after NSAIDs	3 ± 1	32 ± 6	46 ± 7	.256
Effect of NSAIDs	−6 ± 2	−50 ± 5	−22 ± 5	.010[a]
Endometriosis	0 (0%)	2 (12%)	8 (38%)	.137
Leiomyoma[b]	0 (0%)	0 (0%)	1 (5%)	.999
Chronic pelvic pain[b]	0 (0%)	0 (0%)	7 (33%)	.018[a]
Any secondary cause[b]	0 (0%)	2 (12%)	10 (48%)	.034[a]
Days per month of nonmenstrual pelvic pain	0.0 ± 0.0	0.6 ± 0.5	12.4 ± 0.3	.002[a]

NSAID, nonsteroidal antiinflammatory drug; *VAS*, visual analog scale; *VMR*, visceromotor reflex; *NRS*, numeric rating scale.

[a] $P < .05$; [b] One participant with endometriosis has comorbid leiomyoma. Five participants with endometriosis also have comorbid chronic pelvic pain. Any secondary cause includes endometriosis, leiomyoma, or chronic pelvic pain.

Oladosu et al. Evaluating abdominal muscle activity in dysmenorrhea. Am J Obstet Gynecol 2018.

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References

1. Zondervan KT, Yudkin PL, Vessey MP, et al. The community prevalence of chronic pelvic pain in women and associated illness behaviour. Br J Gen Pract 2001;51:541-7.
2. Westling AM, Tu FF, Griffith JW, Hellman KM. The association of dysmenorrhea with noncyclic pelvic pain accounting for psychological factors. Am J Obstet Gynecol 2013;209:422.e1-10.
3. Grace VM, Zondervan KT. Chronic pelvic pain in New Zealand: prevalence, pain severity, diagnoses and use of the health services. Aust N Z J Public Health 2004;28:369-75.
4. Oladosu FA, Tu FF, Hellman KM. Nonsteroidal antiinflammatory drug resistance in dysmenorrhea: epidemiology, causes, and treatment. Am J Obstet Gynecol 2018;218:390-400.
5. Chaudhuri A, Singh A, Dhaliwal L. A randomised controlled trial of exercise and hot water bottle in the management of dysmenorrhoea in school girls of Chandigarh, India. Indian J Physiol Pharmacol 2013;57:114-22.
6. Akin M, Price W, Rodriguez G, Erasala G, Hurley G, Smith RP. Continuous, low-level, topical heat wrap therapy as compared to acetaminophen for primary dysmenorrhea. J Reprod Med 2004;49:739-45.
7. Heggannavar A, Kalekar RS, Ajgaonkar R. Effect of microwave diathermy on primary dysmenorrhea: an experimental study. Int J Physiol Res 2017;5:1802-6.
8. Azima S, Bakhshayesh HR, Kaviani M, Abbasnia K, Sayadi M. Comparison of the Effect

of massage therapy and isometric exercises on primary dysmenorrhea: a randomized controlled clinical trial. J Pediatr Adolesc Gynecol 2015;28:486-91.
9. Dawood MY, Ramos J. Transcutaneous electrical nerve stimulation (TENS) for the treatment of primary dysmenorrhea: a randomized crossover comparison with placebo TENS and ibuprofen. Obstet Gynecol 1990;75:656-60.
10. Huang Q-M, Liu L. Wet needling of myofascial trigger points in abdominal muscles for treatment of primary dysmenorrhoea. Acupunct Med 2014;32:346-9.
11. Chan WY. Prostaglandins and nonsteroidal antiinflammatory drugs in dysmenorrhea. Annu Rev Pharmacol Toxicol 1983;23:131-49.
12. Hellman KM, Yu PY, Oladosu FA, et al. The effects of platelet-activating factor on uterine contractility, perfusion, hypoxia, and pain in mice. Reprod Sci 2018;25:384-94.
13. Woodbury RA, Torpin R. Myometrial physiology and its relation to pelvic pain. JAMA 1947;134:1081-5.
14. Milsom I, Andersch B. Effect of ibuprofen, naproxen sodium and paracetamol on intrauterine pressure and menstrual pain in dysmenorrhoea. Br J Obstet Gynaecol 1984;91:1129-35.
15. Mackenzie J. Remarks on the meaning and mechanism of visceral pain as shown by the study of visceral and other sympathetic (autonomic) reflexes. Br Med J 1906;1:1523-8.
16. Ness TJ, Metcalf AM, Gebhart GF. A psychophysiological study in humans using phasic colonic distension as a noxious visceral stimulus. Pain 1990;43:377-86.
17. Yarnitsky D. Quantitative sensory testing. Muscle Nerve 1997;20:198-204.
18. Hellman KM, Kuhn CS, Tu FF, et al. CINE MRI during spontaneous cramps in women with menstrual pain. Am J Obstet Gynecol 2018;218:506.e1-8.
19. Hjermstad MJ, Fayers PM, Haugen DF, et al. Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage 2011;41:1073-93.
20. Casper RF, Powell AM. Premenstrual syndrome: documentation by a linear analog scale compared with two descriptive scales. Am J Obstet Gynecol 1986;155:862-7.
21. Costantini R, Affaitati G, Wesselmann U, Czakanski P, Giamberardino MA. Visceral pain as a triggering factor for fibromyalgia symptoms in comorbid patients. Pain 2017;158:1925-37.
22. Maquet D, Croisier J-L, Demoulin C, Crielaard J-M. Pressure pain thresholds of tender point sites in patients with fibromyalgia and in healthy controls. Eur J Pain 2004;8:111-7.
23. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175-91.
24. Staud R, Craggs JG, Perlstein WM, Robinson ME, Price DD. Brain activity associated with slow temporal summation of C-fiber evoked pain in fibromyalgia patients and healthy controls. Eur J Pain 2008;12:1078-89.
25. Ness T, Gebhart G. Colorectal distension as a noxious visceral stimulus: physiologic and pharmacologic characterization of pseudoaffective reflexes in the rat. Brain Res 1988;450:153-69.
26. Ness TJ, Lewis-Sides A, Castroman P. Characterization of pressor and visceromotor reflex responses to bladder distention in rats: sources of variability and effect of analgesics. J Urol 2001;165:968-74.
27. Yan T, Liu B, Du D, Eisenach JC, Tong C. Estrogen amplifies pain responses to uterine cervical distension in rats by altering transient receptor potential-1 function. Anesth Analg 2007;104:1246-50.
28. Gebhart GF, Sengupta JN. Evaluation of visceral pain. In: Handbook of methods in gastrointestinal pharmacology. Vol 27. Boca Raton, FL: CRC Press; 1995. p. 359-74.
29. Qian X, Li P, Shi S-Q, Garfield RE, Liu H. Simultaneous recording and analysis of uterine and abdominal muscle electromyographic activity in nulliparous women during labor. Reprod Sci 2017;24:471-7.
30. Unsgaard-Tøndel M, Nilsen TIL, Magnussen J, Vasseljen O. Are fear avoidance beliefs associated with abdominal muscle activation outcome for patients with low back pain? Physiother Res Int 2013;18:131-9.
31. McManis PG, Newall D, Talley NJ. Abdominal wall muscle activity in irritable bowel syndrome with bloating. Am J Gastroenterol 2001;96:1139-42.
32. Tremolaterra F, Villoria A, Azpiroz F, Serra J, Aguadé S, Malagelada J-R. Impaired viscerosomatic reflexes and abdominal-wall dystony associated with bloating. Gastroenterology 2006;130:1062-8.
33. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 2005;114:295-302.
34. Stroman PW, Bosma RL, Cotoi AI, et al. Continuous descending modulation of the spinal cord revealed by functional MRI. PLoS One 2016;(11):e0167317.

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