BMC Women's Health

RESEARCH

Open Access

Exploring the role of negative expectations and emotions in primary dysmenorrhea: insights from a case-control study

Verena Thomann[1], Nadya Gomaa[2], Marina Stang[2], Susanne A. Funke[2] and Karin Meissner[1*]

Abstract

Background Primary dysmenorrhea, characterized by painful menstruation, significantly impacts the quality of life for women worldwide. Negative expectations and associated emotions are known to trigger nocebo effects and may also influence cyclic menstrual pain. In this study, we investigated the role of pain expectations and negative anticipatory emotions as potential contributing factors to hyperalgesia in women with severe menstrual pain, compared to women with absent or mild menstrual pain.

Methods We conducted a prospective case-control study in women with severe menstrual pain due to primary dysmenorrhea, comparing them with age-matched women with absent or mild menstrual pain. Data collection included the Depression, Anxiety, and Stress Scale (DASS-21) at baseline, as well as daily numeric rating scales (NRS) to evaluate pain expectations, anticipatory negative emotions, and daily stress during the 10 days preceding menstruation. Saliva samples were collected to evaluate the Cortisol Awakening Response (CAR) before menstruation, and pain was assessed during the first 3 days of menstruation.

Results Women with high menstrual pain reported significantly higher DASS-21 anxiety levels compared to low-pain controls, although still within the normal range (*median [IQR]*, 3 [2; 5] vs. 1 [1; 3], $p < .05$). In the 10 days preceding menstruation, the high-pain group expected significantly higher maximum pain levels than controls (*median [IQR]*, 8 [7.3; 8.5] vs. 2.1 [1; 3.3], $p < .001$), which aligned with their actual experiences of maximum pain during menstruation (6.5 [4.8; 7.7] vs. 1.2 [0.7; 2.3], $p < .001$). Anticipatory stress (2.1 [0.9; 4.2] vs. 0.2 [0; 0.9], $p < .001$), anticipatory anxiety (0.7 [0.0; 2.3] vs. 0 [0; 0], $p < .001$), anticipatory worry (1.3 [0.4; 2.6] vs. 0.1 [0; 0.3], $p < .001$), and anticipatory anger (0.7 [0; 1.5] vs. 0 [0; 0.2], $p < .01$) were also significantly higher in the high-pain group in the 10 days before menstruation. The CAR showed no significant differences between groups in the days before menstruation. Correlational analyses revealed multiple positive associations between expected pain levels, anticipatory negative emotions, and subsequently perceived levels of menstrual pain in both groups (all p-values < 0.05).

Conclusions This pioneering study supports the hypothesis that cognitive-emotional factors such as heightened pain anticipation and negative emotions intensify menstrual pain severity in primary dysmenorrhea, although causal conclusions cannot be drawn from this observational study. Strategies aimed at optimizing expectations could play a significant role in managing primary dysmenorrhea.

*Correspondence:
Karin Meissner
karin.meissner@hs-coburg.de

Full list of author information is available at the end of the article

Keywords Nocebo effect, Pain perception, Psychological stress, Anticipation, Hydrocortisone, Anxiety

Background

Dysmenorrhea, defined as painful menstruation, is a common and often disabling condition. It involves cramp-like abdominal pain accompanied by symptoms such as nausea, vomiting, diarrhea, and low back pain [1]. In primary dysmenorrhea, menstrual pain occurs without organic pathology and typically starts within 6–12 months after menarche. The pain usually begins with the onset of menstruation and lasts between 8 and 72 h. In secondary dysmenorrhea, the complaints can be traced back to an identified pathology, such as endometriosis, starting at any time after menarche [2].

Approximately 75% of adolescent females and 25–50% of adult women experience menstrual pain [3]. The condition significantly impairs health-related quality of life. The physical discomfort can disrupt sleep patterns, leading to fatigue and exhaustion [4]. Dysmenorrhea frequently results in reduced productivity and increased absenteeism from school or work [5]. In addition, the chronic nature of dysmenorrhea may lead to feelings of frustration, irritability, and mood swings, affecting emotional well-being [6–8].

The reasons for the occurrence of menstrual pain in primary dysmenorrhea are not yet fully understood. A widely accepted hypothesis involves the overproduction or imbalance of prostaglandins in the uterus [9, 10]. Due to the reduction of progesterone in the late luteal phase, an increased release of prostaglandins occurs, leading to vasoconstriction and myometrial contraction. The resulting ischemia or hypoxia is considered the main cause of pain in primary dysmenorrhea [11, 12]. In the long term, peripheral and central sensitization processes may occur, contributing to heightened pain perception in individuals with dysmenorrhea, a phenomenon referred to as visceral hyperalgesia [4].

Several studies suggest a relationship between primary dysmenorrhea and emotional distress [13]. Emotional distress is a recognized risk factor for dysmenorrhea [14]. Furthermore, negative emotions such as anxiety can enhance pain, while pain can amplify emotional distress [4, 15, 16]. But also cognitive factors, such as the expectation of pain, and associated anticipatory anxiety, may play a role [17]. For example, a recent study identified anticipatory anxiety as a factor that exacerbates nocebo hyperalgesia [18]. In the context of medical interventions, such expectation-induced hyperalgesia is referred to as 'nocebo effect'. It is reasonable to assume that cyclic events like menstruation can similarly trigger negative expectations and anticipatory emotions, such as anxiety, leading to an expectation-induced exacerbation of pain. This notion is supported by qualitative studies that report women with dysmenorrhea experience anxiety regarding their menstrual pain [6].

Enhancing knowledge about the potential impact of negative expectations and associated anticipatory negative emotions on the severity of menstrual pain could contribute to better understand the complex nature of dysmenorrhea and its modulation by psychological and physiological factors. Moreover, this knowledge could inform the development of complementary treatment approaches, such as cognitive-behavioral interventions or mindfulness-based strategies, to manage dysmenorrhea by addressing maladaptive pain expectations and associated emotional distress.

The present study aimed to investigate pain expectations and anticipatory negative emotions, specifically anxiety, worry, anger and stress, in women with primary dysmenorrhea. We investigated women with severe menstrual pain (high-pain group) and compared them to women with absent or mild menstrual pain (low-pain group). We hypothesized that women who typically experience high menstrual pain would anticipate more intense menstrual pain and report higher levels of anticipatory negative emotions (worry, stress, anxiety, and anger) in the days before menstruation than women with typically low or absent menstrual pain. Since stress-related activation of the hypothalamus-pituitary-adrenal (HPA) axis has been reported in situations of both anticipatory anxiety [19] and nocebo hyperalgesia [20], we additionally tested whether the hypothesized larger anticipatory stress of women with high menstrual pain would be associated with an increased cortisol awakening response (CAR). The CAR has been shown to be sensitive to anticipatory stress and anxiety [19].

Methods

Study design and setting

We conducted a prospective case-control study to investigate pain expectations and anticipatory negative emotions in 20 women with severe menstrual pain due to primary dysmenorrhea (high-pain group) compared to 20 age-matched (± 2 years) women with absent or mild menstrual pain (low-pain group). Participants were recruited between April and June 2021. Due to the COVID-19 pandemic, all data were collected remotely and by mail. The manuscript was prepared according to the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) criteria [21]. The study protocol was approved by the Ethics Committee of Coburg University (approval number: HC-Meißner-20210324). All participants provided written informed consent.

Participants

To be eligible for the study, women had to be at least 18 years old, have a regular menstrual cycle of approximately 26 to 34 days, and possess sufficient proficiency in the German language to participate in quantitative surveys and qualitative interviews (qualitative results are not reported here). Exclusion criteria comprised the use of hormonal contraceptives in the last 3 months, a diagnosis of secondary dysmenorrhea (e.g., caused by endometriosis, adenomyosis), the use of psychotropic drugs, a diagnosed psychiatric disorder, and current pregnancy or breastfeeding. Participants in the high-pain group were required to report a history of severe menstrual pain ≥ 6 on a 11-point numerical rating scale (NRS) ranging from 0 ('no pain') to 10 ('worst imaginable pain') [22] during the last 3 menstrual cycles. This was assessed by asking the question: *'How would you rate your menstrual pain over the last 3 periods on a scale from 0 to 10?'* [adapted from 23]. Participants in the low-pain group had to report a history of absent or mild menstrual pain ≤ 3 on the same 11-point NRS [24, 25] during the last 3 menstrual cycles. Women with mild menstrual pain have been shown to display almost no daily pain-related restrictions during menstruation [26] and were therefore considered suitable as a control group for this study.

Recruitment took place via the student portal of Coburg University, through messenger services like WhatsApp, as well as through word-of-mouth. Potential study participants were asked to contact one of the authors (VT) and were sent participant information about the study as well as a consent form. During a telephone appointment, potential questions were answered, women were screened for inclusion and exclusion criteria, and sociodemographic and medical data were collected to determine study eligibility, as well as cycle length and the severity of dysmenorrhea.

Procedure

After enrollment, participants were mailed Salivette© tubes (Sarstedt, Nümbrecht, Germany) along with a prepaid return package for collecting and sending back the cortisol samples to Coburg University. Additionally, participants received detailed instructions on saliva sampling and storing as well as data collection in the online diary. Participants were instructed to record the collection time on the saliva tubes, and the timestamps were checked for consistency, indicating good adherence to the protocol. The questionnaires were administered online using QuestorPro software (version 5.1.1, Blubbsoft GmbH, Berlin). Data collection commenced 12 days prior to the expected onset of menstruation, based on individual menstrual cycle data, and concluded on the third day of the following menstruation period. The evaluation started with the assessment of the German version of the Depression, Anxiety, and Stress Scale (DASS-21) [27]. On the same and subsequent days until the onset of menstruation, participants were asked to rate expected menstrual pain, anticipatory negative emotions, and overall stress levels using an online diary. Each morning until the onset of menstruation, participants collected saliva samples to assess the CAR and were instructed to store the samples in the refrigerator until mailing them back to Coburg University. After menstruation onset, participants rated menstrual pain during the first 3 evenings and were asked to note the use of any pain medication.

DASS-21

The DASS-21 [27] is a validated questionnaire to assess negative emotional states over the past week. It comprises 21 items rated on a 4-point Likert scale, ranging from 0 ('does not apply to me at all') to 3 ('applies to me very much, or most of the time'). The 21 items are grouped into 3 subscales (depression, anxiety, and stress), with higher scores indicating more severe depression, anxiety, and/or stress.

Daily numeric rating scales (NRS)

Mean and maximum menstrual pain were assessed using an 11-point NRS, ranging from 0 ('no pain') to 10 ('worst imaginable pain'). Pain-related disability in daily activities was evaluated using an 11-point NRS, ranging from 0 ('not at all') to 10 ('to the highest degree'). 11-point NRS have been recommended as core outcome measures in chronic pain trials [28] as well as for the assessment of expectations [29].

Mean and maximum expected menstrual pain for the upcoming menstruation was assessed using 11-point NRSs, ranging from 0 ('no pain') to 10 ('worst imaginable pain'). Expected pain-related disability in daily activities for the next menstruation was rated using an 11-point NRS, ranging from 0 ('not at all') to 10 ('to the highest degree'). Anticipatory negative emotions (stress, anxiety, worry, anger) were evaluated using 11-point NRSs, with each emotion rated from 0 ('not at all') to 10 ('to the highest degree'), starting with the question: 'To what extent did the thought of your upcoming period elicit the following feelings today?'. The overall stress level was assessed using an 11-point NRS, ranging from 0 ('no stress at all') to 10 ('extremely stressed').

Cortisol awakening response (CAR)

Participants were instructed to collect 2 cortisol saliva samples: one immediately upon waking and the other 30 min later. The standard guideline for morning cortisol collection recommends 3 samples (0 min, 30 min, 45 min) to measure the highest CAR [30]. However, we omitted the third sample at 45 min to reduce participant burden and ensure protocol adherence, given that

previous research indicated that 2 samples were sufficient to detect the CAR [19]. The Salivette© tubes were pre-marked with participant numbers, and participants labeled their samples with the collection times and dates. Participants were instructed to keep the samples cool until shipping. The cortisol analysis was performed at the Institute for Bioanalysis, Coburg University, using a standard Cortisol Saliva ELISA kit (IBL International GmbH, Hamburg, Germany), with positive controls serving as reference values. The ELISA was performed in duplicate for each sample, and the average of the 2 values was used for data analysis. The increase in CAR was calculated by subtracting the cortisol levels at awakening from the levels 30 min after awakening, with a higher increase indicating greater HPA axis activity [19].

Statistical analysis

The sample size was defined a priori, without a formal sample size calculation. Given the exploratory nature of this study, this approach aligns with its objective of identifying potential patterns and generating hypotheses for future research. Diary assessments and the CAR were analyzed for the last 10 days before menstruation, as these data were complete for most of the participants. Since only 1.3% of the diary entries and 1% of the cortisol data were missing, average values from the remaining recorded days of individual participants were used in the statistical analyses. Group comparisons for the NRS ratings were performed using Mann-Whitney U-tests due to violations of the normality assumption, whereas the group differences for the CAR were normally distributed and evaluated using Student's t-test. Group differences for categorical variables were evaluated using Fisher's exact test. Spearman's rho coefficients were calculated to evaluate bivariate correlations between the variables. The level of significance was set at 0.05 (2-sided). No adjustments for multiple comparisons were applied due to the exploratory nature of the study.

Results

Sample

Of the 98 women who contacted the study center, 69 expressed interest in participating and were screened for inclusion and exclusion criteria. Between April and June 2021, 41 women were recruited and started data collection. One woman had to be excluded because her menstruation started just one day after data collection began. Therefore, a total of 20 women with high menstrual pain and 20 age-matched women with low menstrual pain (mean age, 23.9 ± 2.7 SD years; range, 19–30 years) completed the study. 1.3% of the diary entries and 1% of the cortisol data were missing. Specifically, 2 women began their diary entries only 9 days before menstruation, while 2 others started 8 days before. One participant did not complete diary entries on the 2nd day before menstruation. Additionally, 3 women started collecting cortisol samples only 9 days before menstruation, while 1 participant failed to collect cortisol samples on the 5th day before menstruation. 15 out of 20 women with high menstrual pain reported using pain medication (mostly non-steroidal anti-inflammatory drugs) during the first 3 days of menstruation (1 day: $n = 6$, 2 days: $n = 9$). In contrast, 2 out of 20 women with low menstrual pain used pain medication on one day.

Table 1 Sociodemographic and clinical characteristics by study group

		Severe menstrual pain ($n = 20$)	Mild menstrual pain ($n = 20$)	p-value[1]
Age, *median [IQR]*		24 [22; 25.8]	23 [22; 26]	0.763
Highest education level, *n (%)*				0.127
	Intermediate school	1 (5)	0	
	High school	17 (85)	13 (65)	
	Bachelor's degree	2 (10)	7 (35)	
Occupation, *n (%)*				0.605
	Student	19 (95)	17 (85)	
	Employee	1 (5)	2 (10)	
	None	0	1 (5)	
Relationship, *n (%)*				1
	Single	3 (15)	4 (20)	
	In relationship/ married	17 (85)	16 (80)	
Menstrual pain (last 3 months), *11-point NRS, median (IQR)*		7.5 [7; 8]	1.8 [1.1; 2.4]	< 0.001
DASS-21, *median (IQR)*				
	Depression	3.6 [1.3; 7]	2.5 [1; 6.3]	0.269
	Anxiety	3 [2; 5]	1 [1; 3]	0.014
	Stress	6 [3; 10.8]	3 [2; 8.5]	0.149

[1]determined by Mann-Whitney U-test and Fisher's exact test, as appropriate

Abbreviations: IQR, interquartile range; *NRS*, Numeric rating scale

No group differences in sociodemographic characteristics were observed (Table 1). DASS-21 anxiety levels were significantly higher in women with high menstrual pain compared to those with low menstrual pain, albeit still within the normal range, while DASS-21 depression and stress scores did not differ between groups and remained low (Table 1).

Expected and perceived menstrual pain

Over the 10 days preceding menstruation, women with high menstrual pain expected significantly higher mean and maximum pain levels, and greater pain-related disability, for the upcoming menstruation compared to women with low menstrual pain (Table 2). Both mean and maximum pain levels, as well as pain disability during menstruation, were higher in the high-pain group than in the low-pain group (Table 2). Figure 1 illustrates the expected and actual levels of menstrual pain in both groups. The expected levels of menstrual pain were closely aligned with the peak levels of menstrual pain and pain-related disability.

Anticipatory negative emotions

Over the 10 days preceding menstruation, anticipatory stress, anxiety, worry, and anger levels were higher in high-pain group compared to the low-pain group. Particularly in the high-pain group, anticipatory negative emotions increased toward the onset of menses (Fig. 2A-D; Table 2). Considering this increase, we calculated the average levels of anticipatory emotions across both the last 10 days and the last 3 days preceding menstruation. Across both time periods and for all anticipatory emotional ratings, women in the high-pain group anticipated significantly higher emotional distress than those in the low-pain control group (Table 2).

Daily stress levels

Daily stress levels, averaged across the last 10 and last 3 days before menstruation, were significantly higher in the high-pain group compared to the low-pain control group (Table 2; Fig. 2E).

CAR

The CAR fluctuated before menstruation in both study groups (Fig. 2F). Average values across the last 10 and the last 3 days before menstruation did not differ between the high-pain and the low-pain groups (Table 2).

Explorative correlational analyses

Exploratory bivariate correlations are presented separately for the high-pain and the low-pain groups in Tables 3 and 4, respectively. In the high-pain group, the peak levels of mean and maximum menstrual pain and pain-related disability during the first 3 menstruation days exhibited multiple positive associations with expected pain levels and anticipatory negative emotions

Table 2 Group differences of outcome variables

		High-pain group ($n=20$)	Low-pain group ($n=20$)	*p*-value	High-pain group ($n=20$)	Low-pain group ($n=20$)	*p*-value
Menstrual pain, *median [IQR]*		Menstrual averages (days 1–3)			Menstrual peaks (days 1–3)		
	Mean pain	4.7 [3.1; 6.2]	0.7 [0; 1]	< 0.001	6.5 [5; 7]	1 [0; 2]	< 0.001
	Maximum pain	6.5 [4.8; 7.7]	1.2 [0.7; 2.3]	< 0.001	8 [8; 9]	2 [1; 3.8]	< 0.001
	Pain disability	4.3 [2.5; 5.3]	0.5 [0; 0.9]	< 0.001	6 [4.3; 8]	1 [0; 1]	< 0.001
Pain expectation, *median [IQR]*		Pre-Menstruation averages (10 days)			Pre-Menstruation averages (3 days)		
	Mean pain	6.8 [5.7; 7.2]	1 [0; 1.3]	< 0.001	6.5 [6; 7.8]	1 [0; 1]	< 0.001
	Maximum pain	8 [7.3; 8.5]	2.1 [1; 3.3]	< 0.001	8 [7.4; 8.8]	2 [1; 3]	< 0.001
	Pain disability	6.6 [5.3; 7.2]	1 [0; 1.5]	< 0.001	6.7 [5.3; 7.8]	1 [0; 1.3]	< 0.001
Anticipatory emotions, *median [IQR]*		Pre-Menstruation averages (10 days)			Pre-Menstruation averages (3 days)		
	Stress	2.1 [0.9; 4.2]	0.2 [0; 0.9]	< 0.001	3.3 [1.5; 5.7]	0 [0; 1.2]	< 0.001
	Anxiety	0.7 [0.0; 2.3]	0 [0; 0]	< 0.001	0.8 [0; 4.3]	0 [0; 0]	0.006
	Worry	1.3 [0.4; 2.6]	0.1 [0; 0.3]	< 0.001	2 [0.5; 4.9]	0.3 [0; 0.6]	< 0.001
	Anger	0.7 [0; 1.5]	0 [0; 0.2]	0.003	1.3 [0; 3.7]	0 [0; 0]	< 0.001
Stress measures		Pre-Menstruation averages (10 days)			Pre-Menstruation averages (3 days)		
	General stress level, *median [IQR]*	4.2 [2.7; 4.7]	2.9 [1.1; 3.3]	0.007	4.3 [2.7; 5.3]	2.7 [1.3; 3.6]	0.023
	CAR, *mean [95% CI]*	0.17 [0.12; 0.22]	0.15 [0.04; 0.27]	0.883	0.20 [0.12; 0.28]	0.16 [0.03; 0.29]	0.609

Abbreviations: DASS, Depression, Anxiety, and Stress Scale*; IQR*, interquartile range; *CAR*, cortisol awakening response; *CI*, confidence interval

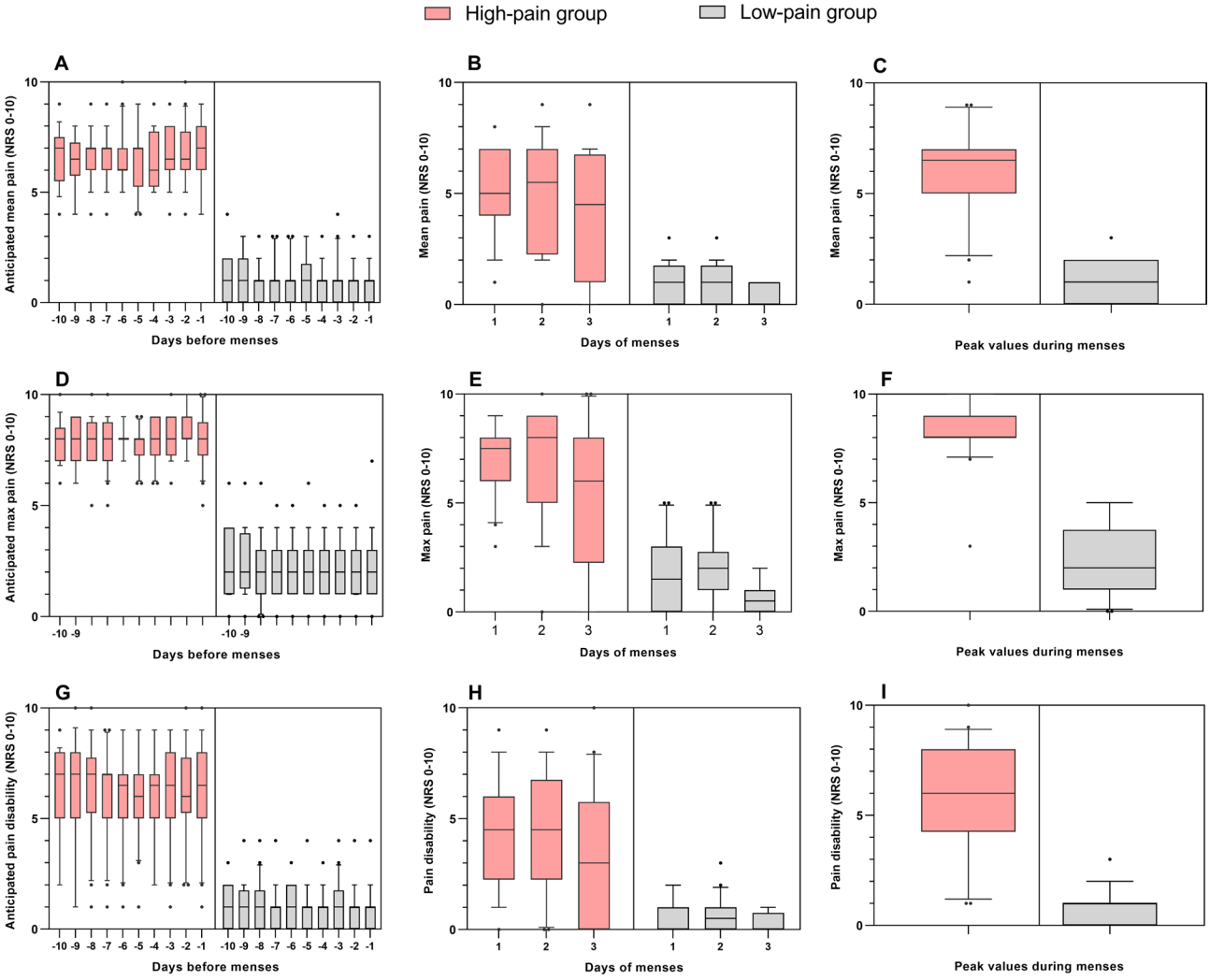

Fig. 1 Trajectories of expected menstrual pain during the 10 days before menstruation (left), actual menstrual pain during the first 3 days of menstruation (middle), and peak menstrual pain (right) in the high-pain and low-pain groups, respectively. **A**-**C**, mean pain; **D**-**F**, maximum pain; **G**-**I**, pain disability. Boxplots display the median (horizontal line), the interquartile range (the box), and the 10th and 90th quartiles (whiskers). *NRS*, numeric rating scale

during the last 3 days before menstruation. Similar trends were observed in the low-pain control group. Figure 3 illustrates the correlations between peak levels of mean menstrual pain and (A) expected mean pain, (B) anticipatory stress, and (C) anticipatory worry for both groups. The CAR was not correlated with the other variables in any group.

Discussion

This prospective case-control study revealed that women with severe menstrual pain exhibited higher levels of expectations of pain and anticipatory negative emotions compared with women with no or mild menstrual pain. Expectation levels remained fairly stable in the 10 days before menstruation. In contrast, menstruation-related anticipatory emotions intensified particularly in the high-pain group as the onset of menstruation approached.

Our findings of high anticipatory stress and anxiety in women with severe menstrual pain corroborate previous qualitative studies suggesting that women develop a fear of impending menstrual pain [6, 7]. Moreover, women with severe dysmenorrhea in our study exhibited increased anticipatory anger and worry as menstruation approached, which complements other studies pointing out women's frustration with the unpredictability of planned activities and the limitations they experience during menstruation [6, 8].

Nocebo hyperalgesia, induced by negative expectations, is closely linked to anticipatory stress and anxiety [17, 31]. The anticipation of pain is known to trigger state anxiety, which in turn facilitates pain perception through cholecystokinergic mechanisms [32]. Therefore, the high expectations of menstrual pain in women with severe primary dysmenorrhea, accompanied by anticipatory stress

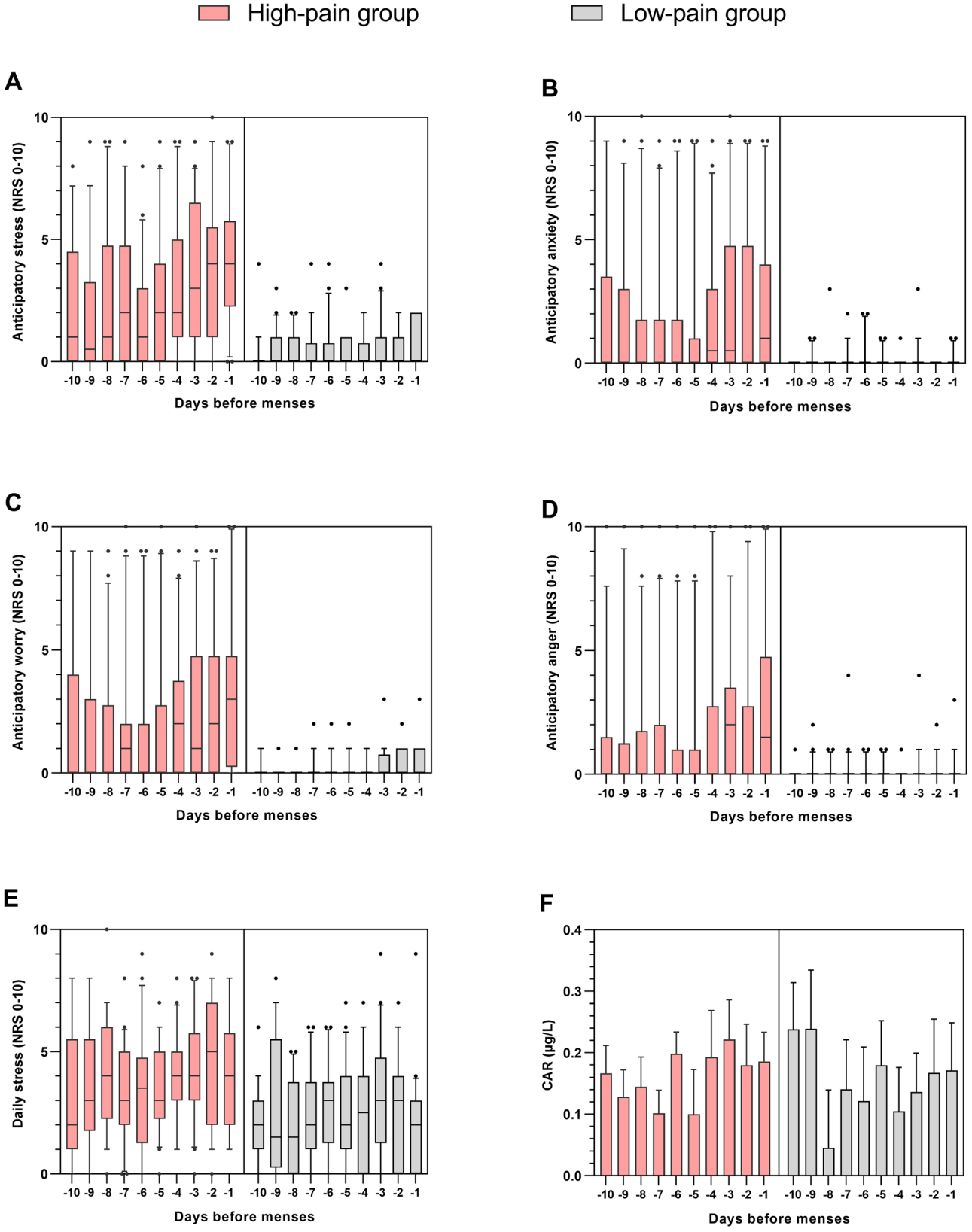

Fig. 2 Trajectories of anticipatory stress (**A**), anxiety (**B**), worry (**C**) and anger (**D**), daily stress (**E**), and CAR (**F**) during the 10 days before menstruation in the high-pain and low-pain groups, respectively. Boxplots display the median (horizontal line), the interquartile range (the box), and the 10th and 90th quartiles (whiskers). CAR values are means (SE). *CAR*, cortisol awakening response; *NRS*, numeric rating scale

Table 3 Spearman's Rho correlation coefficients between actual pain (peak values during menstruation days 1–3) and pre-menstruation 3-day averages of anticipated pain, anticipatory emotions, general stress, and the cortisol awakening response (CAR) in the high-pain group ($n = 20$). $^{***}p < .001$; $^{**}p < .01$; $^{*}p < .05$

	Mean menstrual pain (peak)	Maximum menstrual pain (peak)	Menstrual pain disability (peak)	Expected mean menstrual pain	Expected maximum menstrual pain	Expected menstrual pain disability	Anticipatory stress	Anticipatory anxiety	Anticipatory worry	Anticipatory anger	General stress
Expected mean menstrual pain	**0.66****	0.44	**0.45***	1							
Expected maximum menstrual pain	**0.52***	0.36	0.15	**0.78*****	1						
Expected menstrual pain disability	0.35	−0.04	0.44	**0.63****	**0.47***	1					
Anticipatory stress	**0.54***	0.42	**0.45***	**0.74*****	**0.72*****	**0.59****	1				
Anticipatory anxiety	**0.58****	**0.55***	0.16	0.37	**0.45***	0.3	**0.56***	**1**			
Anticipatory worry	**0.71*****	**0.59****	**0.56****	**0.56***	**0.53***	0.37	**0.74*****	**0.77*****	**1**		
Anticipatory anger	**0.62****	**0.63****	0.37	0.40	0.42	0.15	**0.6*****	**0.59****	**0.69*****	1	
General stress	0.02	0.0	0.29	0.36	0.4	**0.47***	**0.45***	-0.01	0.21	0.03	1
CAR	0.12	0.02	0.32	−0.11	-0.2	0.09	0.0	-0.37	-0.1	0.1	0.33

Table 4 Spearman's Rho correlation coefficients between actual pain (peak values during menstruation days 1–3) and pre-menstruation 3-day averages of anticipated pain, anticipatory emotions, general stress, and the cortisol awakening response (CAR) in the low-pain group ($n = 20$). $^{***}p < .001$; $^{**}p < .01$; $^{*}p < .05$

	Mean menstrual pain (peak)	Maximum menstrual pain (peak)	Menstrual pain disability (peak)	Expected mean menstrual pain	Expected maximum menstrual pain	Expected menstrual pain disability	Anticipatory stress	Anticipatory anxiety	Anticipatory worry	Anticipatory anger	General stress
Expected mean menstrual pain	**0.88*****	**0.81*****	**0.86*****	1							
Expected maximum menstrual pain	**0.65****	**0.83*****	**0.63****	**0.79*****	1						
Expected menstrual pain disability	**0.67****	**0.64****	**0.71*****	**0.79*****	**0.56****	1					
Anticipatory stress	0.39	0.43	**0.53***	0.40	0.28	**0.51***	1				
Anticipatory anxiety	**0.46***	**0.49***	**0.64****	**0.51***	0.38	**0.47***	0.40	1			
Anticipatory worry	**0.49***	0.44	**0.49***	**0.53***	**0.45***	**0.60****	**0.61****	0.44	**1**		
Anticipatory anger	**0.48***	0.24	0.52*	0.41	0.24	**0.51***	**0.75*****	0.41	**0.47***	1	
General stress	0.32	**0.62****	**0.46***	0.39	**0.49***	0.37	**0.50***	0.40	0.41	0.07	1
CAR	−0.14	−0.39	−0.17	−0.27	−0.41	−0.43	−0.27	0.13	0.01	−0.12	−0.22

and anxiety, supports the notion that anticipatory mechanisms could also contribute to the severity of menstrual pain. Women suffering from primary dysmenorrhea typically have a history of menstrual pain [2]. In addition, individual experiences during the first menstruation can already be formative, leading to a long-term negative attitude towards menstruation [33]. In addition to negative pain experiences, pain expectations could also be driven by negative suggestions from peers and family members about menstruation, as well as by observing menstrual pain-related behaviors in others [31].

Considering the recurrent pattern of dysmenorrhea, the interplay among expectations, anticipatory emotions, and menstrual pain could create a vicious cycle: Heightened expectations of intense pain amplify anticipatory negative emotions, which in turn, increase the perception of pain, leading to reinforced negative expectations, and so on. This process aligns with predictive coding models, which suggest that the brain actively interprets sensory input based on prior experiences, potentially biasing pain perception toward heightened intensity [34]. Similarly, central sensitization mechanisms may contribute to long-term pain chronification in some individuals,

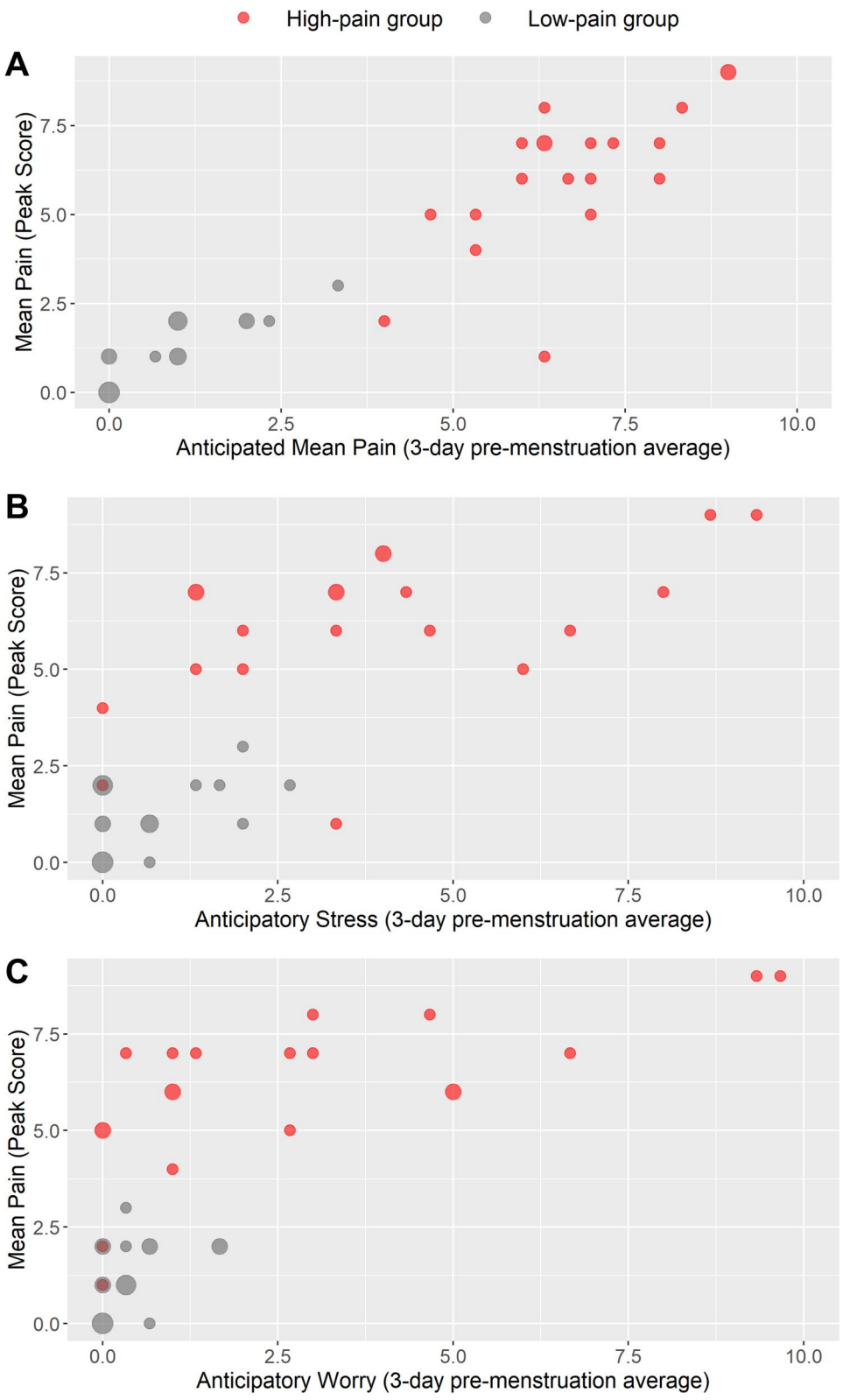

Fig. 3 Correlations between mean menstrual pain (peak values) for the high-pain group ($n = 20$; red circles) and the low-pain group ($n = 20$; grey circles) and (**A**) anticipated mean pain (3-day pre-menstruation average), (**B**) anticipatory stress (3-day pre-menstruation average), and (**C**) anticipatory worry (3-day pre-menstruation average). Bubble size corresponds to the number of overlapping data points. All ratings were assessed using 11-point numeric rating scales. For Spearman's rho correlation coefficients and additional relationships, see Tables 3 and 4

as repeated exposure to dysmenorrhea-related pain can lead to visceral hyperalgesia at a physiological level [35]. These mechanisms highlight how anticipatory processes might not only influence acute pain perception but also facilitate the transition from recurrent to chronic pain in some women, emphasizing the need for early interventions targeting, among other factors, maladaptive pain expectations.

Several studies have demonstrated that nocebo hyperalgesia is linked to the activation of the hypothalamus-pituitary-adrenal (HPA) axis. For instance, the oral administration of a placebo pill, when accompanied by verbal suggestions of increased pain, has been shown to trigger the release of adrenocorticotropic hormone and cortisol [36]. Likewise, participants with multiple adverse events after the mere suggestion of side effects showed an activation of the HPA axis [37]. It is important to note, however, that activation of the HPA axis is not consistently reported in the nocebo literature [38]. In the context of dysmenorrhea, the anticipation of pain accompanied by negative emotions could similarly trigger cortisol release. However, our findings did not confirm an increase in the CAR, a validated measure of anticipatory stress and anxiety [19]. This absence of evidence may indicate either a true lack of an anticipatory cortisol response or reduced reliability due to the use of two instead of three cortisol measurements, which was chosen to minimize participant burden and ensure protocol adherence. Although previous research suggests that two samples are generally sufficient to detect the CAR [19], the maximum morning increase may have been missed in some cases, and more rigorous CAR protocols [30] may yield different results. Additionally, individual variability in cortisol reactivity could have obscured group-level patterns, further contributing to the absence of significant differences. Alternatively, the stress levels experienced before menstruation might not have been sufficient to elicit a cortisol response. Furthermore, an altered CAR may occur only during the first months after menarche, when the memory of menstrual pain develops. Once primary dysmenorrhea is established, expectation-related hyperalgesia may manifest without eliciting a significant cortisol response.

An additional finding of our study was that women with severe menstrual pain exhibited higher levels of general stress and anxiety compared to participants with mild or no menstrual pain. This finding is consistent with previous research indicating increased stress and anxiety levels in women with primary dysmenorrhea [13]. Moreover, a prior study reported a direct correlation between overall levels of anxiety and depression and the severity of dysmenorrhea [39]. Furthermore, evidence suggests a significant correlation between stress perceived in the preceding menstrual cycle and the occurrence of dysmenorrhea in the following cycle [14].

This study has several potential limitations. First, the screening question did not specify whether menstrual pain referred to average or maximum pain, and data collection was limited to a single menstrual cycle. Future studies should assess pain during a baseline period to confirm the presence or absence of dysmenorrhea, using the same pain scales as in the evaluation period, and consider a longer evaluation period. Second, the study did not include a gynecological investigation, which was difficult to conduct during the COVID-19 pandemic. As a result, the self-reported history of dysmenorrhea could have been inaccurate, and some participants may have had undiagnosed secondary dysmenorrhea. Third, the use of pain medication, primarily by women in the high-pain group, was not prohibited for ethical reasons, which may have led to an underestimation of dysmenorrhea intensity in the present study. Fourth, it should be noted that the present study design does not allow for determining causal effects of anticipation. The effects of past experiences, potential pain chronification processes, and current anticipatory effects cannot be clearly distinguished in this context. Fifth, the levels of stress and negative emotions during the COVID-19 pandemic may not have been representative in either group. While stress levels in young people were generally elevated during this time [40], women with dysmenorrhea may have experienced less stress than usual, as reduced opportunities for social activities and the shift to home office likely alleviated the stress associated with pain-related absenteeism from schools and universities [5, 41, 42], a point further confirmed in our interviews. Sixth, the generalizability of the study may be limited due to the predominant inclusion of students, resulting in socioeconomic and educational homogeneity within the sample. Future studies should employ more diverse recruitment strategies to enhance sample representativeness. Seventh, the increase of anticipatory emotions in women with severe dysmenorrhea before menstruation could partially be due to premenstrual syndrome (PMS), which is associated with affective symptoms such as anger and anxiety [43] but has not been assessed in the present study. Eighth, we did not measure levels of progesterone and estradiol as potential modulators of mood and emotions during the menstrual cycle [44]. Finally, it is important to note that expectation-related influences may also be present in individuals in the control group with mild menstrual pain, even though mild dysmenorrhea typically does not result in daily restrictions [26]. Future case-control studies should consider including control groups without any menstrual pain.

Conclusions

To our knowledge, this is the first study to explore the potential role of expectation-related processes in participants with menstrual pain. We identified several parallels between nocebo effects and menstruation-related anticipatory cognitions and emotions. In particular, menstrual pain was preceded by elevated expectations of pain and a marked increase in anticipatory stress and anxiety as menstruation approached. These observations lend support to the hypothesis that menstrual pain in women with severe dysmenorrhea may be enhanced by expectation-related mechanisms. However, given the exploratory nature of the study and the small student sample, these findings should be interpreted with caution.

Beyond conventional treatments such as painkillers and hormonal medications, current approaches for women with primary dysmenorrhea include, for example, the application of heat [45], acupuncture [46], and physical activity [5]. Our results suggest that treatment strategies to optimize pain-related expectations and associated emotions could also be considered. Expectation management strategies [47] and the use of open-label placebos [48] could help reframe anticipatory pain beliefs, while cognitive behavioral therapy (CBT) has been shown to be effective in reducing pain-related distress and maladaptive cognitions [49]. Similarly, mindfulness-based stress reduction and other relaxation techniques can support emotional regulation and reduce stress reactivity [50], which in turn could help mitigate the impact of anticipatory emotions on pain perception.

Prospective cohort studies could provide valuable insights into the development of menstrual pain in the year after menarche. Additionally, experimental studies manipulating expectations and emotional states could help disentangle causal mechanisms underlying these associations. Incorporating biological markers, such as stress hormone responses or neuroimaging techniques, may further elucidate the physiological pathways linking anticipatory emotions with menstrual pain, ultimately contributing to a more comprehensive understanding of pain modulation in dysmenorrhea.

Abbreviations

CAR	Cortisol Awakening Response
DASS-21	Depression, Anxiety, and Stress Scale
HPA	Hypothalamus-Pituitary-Adrenal
NRS	Numeric Rating Scale
PMS	Premenstrual Syndrome

Author contributions

VT and KM designed the study. VT acquired the data. VT, NG and KM analyzed the data. NG performed the cortisol analyses, MS and SAF supervised the biochemical analyses. KM drafted the manuscript. All authors contributed to data interpretation and approved the final manuscript.

Funding

The conduct of the study was supported in part by funds from the Schweizer-Arau Foundation to KM.

Data availability

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Coburg University (approval number: HC-Meißner-20210324). All participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Institute for Applied Health Sciences, Faculty of Applied Natural Sciences and Health, Coburg University of Applied Sciences and Arts, Coburg, Germany
[2]Institute for Bioanalysis, Faculty of Applied Natural Sciences and Health, Coburg University of Applied Sciences and Arts, Coburg, Germany

Received: 4 April 2024 / Accepted: 6 May 2025
Published online: 21 May 2025

References

1. Harada T. Dysmenorrhea and endometriosis in young women. Yonago Acta Med. 2013;56(4):81.
2. Proctor MML, Farquhar CM. Dysmenorrhoea. *BMJ clinical evidence* 2007, 2007.
3. Latthe P, Latthe M, Say L, Gülmezoglu M, Khan KS. WHO systematic review of prevalence of chronic pelvic pain: a neglected reproductive health morbidity. BMC Public Health. 2006;6(1):1–7.
4. Iacovides S, Avidon I, Baker FC. What we know about primary dysmenorrhea today: a critical review. Hum Reprod Update. 2015;21(6):762–78.
5. Armour M, Smith CA, Steel KA, Macmillan F. The effectiveness of self-care and lifestyle interventions in primary dysmenorrhea: a systematic review and meta-analysis. BMC Complement Altern Med. 2019;19(1):1–16.
6. Allyn K, Evans S, Seidman LC, Payne LA. Tomorrow, i'll be fine: impacts and coping mechanisms in adolescents and young adults with primary dysmenorrhoea. J Adv Nurs. 2020;76(10):2637–47.
7. Berger B, Böning A, Martin H, Fazeli A, Martin D, Vagedes J. Personal perception and body awareness of dysmenorrhea and the effects of rhythmical massage therapy and heart rate variability biofeedback—A qualitative study in the context of a randomized controlled trail. Complement Ther Med. 2019;45:280–8.
8. Fernández-Martínez E, Abreu-Sánchez A, Pérez-Corrales J, Ruiz-Castillo J, Velarde-García JF, Palacios-Ceña D. Living with pain and looking for a safe environment: A qualitative study among nursing students with dysmenorrhea. Int J Environ Res Public Health. 2020;17(18):6670.
9. Morrow C. EH Naumburg 2009 Dysmenorrhea. Prim Care: Clin Office Pract 36 1 19–32.
10. Kawabata A. Prostaglandin E2 and pain—an update. Biol Pharm Bull. 2011;34(8):1170–3.
11. Szmidt MK, Granda D, Sicinska E, Kaluza J. Primary dysmenorrhea in relation to oxidative stress and antioxidant status: a systematic review of case-control studies. Antioxidants. 2020;9(10):994.
12. Dawood MY. Primary dysmenorrhea: advances in pathogenesis and management. Obstet Gynecol. 2006;108(2):428–41.
13. Bajalan Z, Moafi F, MoradiBaglooei M, Alimoradi Z. Mental health and primary dysmenorrhea: a systematic review. J Psychosom Obstet Gynecol. 2019;40(3):185–94.
14. Wang L, Wang X, Wang W, Chen C, Ronnennberg A, Guang W, Huang A, Fang Z, Zang T, Xu X. Stress and dysmenorrhoea: a population based prospective study. Occup Environ Med. 2004;61(12):1021–6.
15. Pakpour AH, Kazemi F, Alimoradi Z, Griffiths MD. Depression, anxiety, stress, and dysmenorrhea: a protocol for a systematic review. Syst Reviews. 2020;9(1):1–6.

16. Blackburn-Munro G, Blackburn-Munro R. Chronic pain, chronic stress and depression: coincidence or consequence? J Neuroendocrinol. 2001;13(12):1009–23.
17. Rooney T, Sharpe L, Todd J, Richmond B, Colagiuri B. The relationship between expectancy, anxiety, and the Nocebo effect: a systematic review and meta-analysis with recommendations for future research. Health Psychol Rev. 2023;17(4):550–77.
18. Rooney T, Sharpe L, Todd J, Livesey E, Colagiuri B. Understanding the role of expectancy, anticipatory anxiety, and attention Bias in Nocebo hyperalgesia: A Gaze-Contingent attention Bias modification study. J Pain. 2024;25(4):946–61.
19. Wetherell MA, Lovell B, Smith MA. The effects of an anticipated challenge on diurnal cortisol secretion. Stress. 2015;18(1):42–8.
20. Blasini M, Corsi N, Klinger R, Colloca L. Nocebo and pain: an overview of the Psychoneurobiological mechanisms. Pain Rep. 2017;2(2):e585.
21. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, Initiative S. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Int J Surg. 2014;12(12):1495–9.
22. Woo A, Lechner B, Fu T, Wong CS, Chiu N, Lam H, Pulenzas N, Soliman H, DeAngelis C, Chow E. Cut points for mild, moderate, and severe pain among cancer and non-cancer patients: a literature review. Ann Palliat Med. 2015;4(4):176–83.
23. Ameade EK, Mohammed B. Menstrual pain assessment: comparing verbal rating scale (VRS) with numerical rating scales (NRS) as pain measurement tools. Int J Womens Health Wellness. 2016;2:017.
24. Huang QM, Liu L. Wet needling of myofascial trigger points in abdominal muscles for treatment of primary dysmenorrhoea. Acupunct Med. 2014;32(4):346–9.
25. Mizuta R, Maeda N, Tashiro T, Suzuki Y, Oda S, Komiya M, Urabe Y. Quality of life by dysmenorrhea severity in young and adult Japanese females: A web-based cross-sectional study. PLoS ONE. 2023;18(3):e0283130.
26. Orhan C, Çelenay ŞT, Demirtürk F, Özgül S, Üzelpasaci E, Akbayrak T. Effects of menstrual pain on the academic performance and participation in sports and social activities in Turkish university students with primary dysmenorrhea: A case control study. J Obstet Gynecol Res. 2018;44(11):2101–9.
27. Nilges P, Essau C. Depression, anxiety and stress scales: DASS—A screening procedure not only for pain patients. Der Schmerz. 2015;29:649–57.
28. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1–2):9–19.
29. Rief W, Nestoriuc Y, Mueller EM, Hermann C, Schmidt K, Bingel U. Generic rating scale for previous treatment experiences, treatment expectations, and treatment effects (GEEE). PsychArchives. 2021. https://doi.org/10.23668/psycharchives.4717
30. Stalder T, Kirschbaum C, Kudielka BM, Adam EK, Pruessner JC, Wüst S, Dockray S, Smyth N, Evans P, Hellhammer DH. Assessment of the cortisol awakening response: expert consensus guidelines. Psychoneuroendocrinology. 2016;63:414–32.
31. Colloca L, Barsky AJ. Placebo and Nocebo effects. N Engl J Med. 2020;382(6):554–61.
32. Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: unraveling the mechanisms of the Nocebo effect. Neuroscience. 2007;147(2):260–71.
33. McPherson ME, Korfine L. Menstruation across time: menarche, menstrual attitudes, experiences, and behaviors. Women's Health Issues. 2004;14(6):193–200.
34. Song Y, Yao M, Kemprecos H, Byrne A, Xiao Z, Zhang Q, Singh A, Wang J, Chen ZS. Predictive coding models for pain perception. J Comput Neurosci. 2021;49(2):107–27.
35. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2–15.
36. Benedetti F, Amanzio M, Vighetti S, Asteggiano G. The biochemical and neuroendocrine bases of the hyperalgesic Nocebo effect. J Neurosci. 2006;26(46):12014–22.
37. Benedetti F, Amanzio M, Giovannelli F, Craigs-Brackhahn K, Shaibani A. Hypothalamic-Pituitary-Adrenal activity in adverse events reporting after placebo administration. Clin Pharmacol Ther. 2021;110(5):1349–57.
38. Thomaidou MA, Peerdeman KJ, Koppeschaar MI, Evers AW, Veldhuijzen DS. How negative experience influences the brain: a comprehensive review of the Neurobiological underpinnings of Nocebo hyperalgesia. Front NeuroSci. 2021;15:652552.
39. Sahin N, Kasap B, Kirli U, Yeniceri N, Topal Y. Assessment of anxiety-depression levels and perceptions of quality of life in adolescents with dysmenorrhea. Reproductive Health. 2018;15(1):1–7.
40. Varma P, Junge M, Meaklim H, Jackson ML. Younger people are more vulnerable to stress, anxiety and depression during COVID-19 pandemic: A global cross-sectional survey. Prog Neuropsychopharmacol Biol Psychiatry. 2021;109:110236.
41. Banikarim C, Chacko MR, Kelder SH. Prevalence and impact of dysmenorrhea on Hispanic female adolescents. Arch Pediatr Adolesc Med. 2000;154(12):1226–9.
42. Söderman L, Edlund M, Marions L. Prevalence and impact of dysmenorrhea in Swedish adolescents. Acta Obstet Gynecol Scand. 2019;98(2):215–21.
43. Hofmeister S, Bodden S. Premenstrual syndrome and premenstrual dysphoric disorder. Am Family Phys. 2016;94(3):236–40.
44. Kornstein SG, Harvey AT, Rush AJ, Wisniewski SR, Trivedi MH, Svikis DS, McKenzie ND, Bryan C, Harley R. Self-reported premenstrual exacerbation of depressive symptoms in patients seeking treatment for major depression. Psychol Med. 2005;35(5):683–92.
45. Jo J, Lee SH. Heat therapy for primary dysmenorrhea: A systematic review and meta-analysis of its effects on pain relief and quality of life. Sci Rep. 2018;8(1):16252.
46. Woo HL, Ji HR, Pak YK, Lee H, Heo SJ, Lee JM, Park KS. The efficacy and safety of acupuncture in women with primary dysmenorrhea: A systematic review and meta-analysis. Med (Baltim). 2018;97(23):e11007.
47. Rief W, Shedden-Mora MC, Laferton JA, Auer C, Petrie KJ, Salzmann S, Schedlowski M, Moosdorf R. Preoperative optimization of patient expectations improves long-term outcome in heart surgery patients: results of the randomized controlled PSY-HEART trial. BMC Med. 2017;15(1):1–13.
48. von Wernsdorff M, Loef M, Tuschen-Caffier B, Schmidt S. Effects of open-label placebos in clinical trials: a systematic review and meta-analysis. Sci Rep. 2021;11(1):3855.
49. Williams ACC, Fisher E, Hearn L, Eccleston C. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev. 2020;8(8):CD007407.
50. Andersen E, Geiger P, Schiller C, Bluth K, Watkins L, Zhang Y, Xia K, Tauseef H, Leserman J, Girdler S, et al. Effects of Mindfulness-Based stress reduction on experimental pain sensitivity and cortisol responses in women with early life abuse: A randomized controlled trial. Psychosom Med. 2021;83(6):515–27.

Publisher's note