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Comprehensive review

Ovarian hormones and chronic pain: A comprehensive review

Samah Hassan [a,*], Abi Muere [b], Gillian Einstein [b,c]

[a] Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada
[b] Department of Psychology, University of Toronto, Toronto, ON, Canada
[c] Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

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ABSTRACT

Most chronic noncancer pain (CNCP) conditions are more common in women and have been reported to worsen, particularly during the peak reproductive years. This phenomenon suggests that ovarian hormones might play a role in modulating CNCP pain. To this end, we reviewed human literature aiming to assess the potential role of ovarian hormones in modulating the following CNCP conditions: musculoskeletal pain, migraine headache, temporal mandibular disorder, and pelvic pain. We found 50 relevant clinical studies, the majority of which demonstrated a correlation between hormone changes or treatments and pain intensity, threshold, or symptoms. Taken together, the findings suggest that changes in hormonal levels may well play a role in modulating the severity of CNCP conditions. However, the lack of consistency in study design, methodology, and interpretation of menstrual cycle phases impedes comparison between the studies. Thus, while the literature is highly suggestive of the role of ovarian hormones in modulating CNCP conditions, serious confounds impede a definitive understanding for most conditions except menstrual migraine and endometriosis. It may be that these inconsistencies and the resulting lack of clarity have contributed to the failure of hormonal effects being translated into medical practice for treatment of CNCP conditions.

1. Introduction

There is a wealth of literature suggesting that there are sex differences in the perception and experience of pain, which were not detected previously, leading to the understanding that women are more sensitive to experimentally induced pain and tend to have lower pain thresholds than men [79,85,120]. In the field of chronic pain, there has been a growing recognition that many chronic noncancer pain (CNCP) conditions occur more frequently in women [14,62,109]. CNCP is a set of clinical conditions characterized by pain that persists despite removal of any stimulus and apparent healing of tissue injury, or pain that arises in the absence of any detectable damage with no relation to cancer [9,50,73,90,94]. CNCP conditions include: musculoskeletal pain (MSP) (eg, fibromyalgia, rheumatoid arthritis [RA]); migraine headache; temporomandibular disorder (TMD); and chronic pelvic pain (eg, irritable bowel syndrome [IBS], endometriosis, and interstitial cystitis). Most of these CNCP conditions display significant increases in prevalence between puberty and menopause, that is, in the reproductive years [67], suggesting that ovarian hormones may be responsible for the observed sex differences.

As a result, researchers have begun to investigate the influence of both ovarian hormone level and fluctuation on pain sensation. These studies provide evidence detailing how variations in pain perception and pain ratings are related to ovarian hormones. Based on their findings, some have concluded that sex differences in pain responses might be attributed to the fluctuation of ovarian hormones across the menstrual cycle [33,85]. In order to provide insights into what is and is not known about CNCP perception and ovarian hormones, we first provide an overview of the menstrual cycle and the associated changes in the levels of ovarian hormones. We then discuss possible mechanisms through which ovarian hormones might modulate pain. Finally, we review the existing literature regarding the influence of ovarian hormones on CNCP.

2. Ovarian hormones and the menstrual cycle

Ovarian hormones are luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogens, and progestagens. Levels

* Corresponding author. Address: Institute of Medical Sciences, University of Toronto, 100 St. George Street, Toronto, ON M5S 3G3, Canada. Tel.: +1 416 995 4003.
E-mail address: sam.hassan@mail.utoronto.ca (S. Hassan).

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of these hormones change over approximately 28 days, leading to the maturation of a set of oocytes, or eggs, and the ultimate release of one (the ovarian cycle). The menstrual cycle involves the concomitant changes in the uterine lining, which, if the egg is not fertilized, is shed, resulting in menses (Fig. 1). The ovarian and menstrual cycles are under the control of the hypothalamic/pituitary/ovarian axis [31]. The regular release of ovarian hormones requires the coordinated activity of: the hypothalamus, which secretes gonadotropin-releasing hormone (GnRH); the pituitary, which secretes LH and FSH; and the ovary, which secretes estrogen and progestagens. Based on the 2 observable events, ovulation and the shedding of the uterine lining, the menstrual cycle is commonly divided into 3 phases: menses, the follicular phase, and the luteal phase. The average length of the menstrual cycle is 28 days, with a range of 25-32 days [28,31,39].

Menstrual cycles are counted from the first day of the shedding of the uterine lining (menses, menstrual bleeding). After menses ends, the follicular phase starts, in which both FSH and LH are secreted, and estrogen gradually increases, peaking just before ovulation. Around mid-cycle, a peak in LH leads to the release of small amounts of progestagens. Ultimately, the follicle ruptures, resulting in ovulation and the beginning of the luteal phase. Shortly after ovulation, the corpus luteum forms and itself secretes large amounts of progestagens. Progestagens peak during the mid-luteal phase with estrogens increasing as well, though this increase is not as high as it was in the follicular phase. These increasing levels of estrogen and progestagens provide negative feedback to the pituitary, resulting in decreased secretion of LH and FSH across the luteal phase. This, in turn, decreases secretion of estrogen and progestagens, which, in the absence of fertilization, leads to the shedding of the uterine lining, menses, and a new menstrual cycle [28,31,39].

Because menses, itself, is observable, the menstrual cycle is often used as a proxy for the ovarian cycle, with assumptions being made about levels of hormones secreted at the different phases. However, it is well established that there are both inter- and intra-subject variations in the length of the total cycle as well as actual amounts of estrogens and progestagens secreted [11].

3. Ovarian hormones and mechanisms of pain modulation

Although the mechanisms and exact dynamics by which ovarian hormones modulate pain remain unclear, ovarian hormones (especially estrogens) are known to play a role at key points along the pain pathway, including: 1) primary afferent nerve fibres where they might modulate signal transduction and the transmission of nociception [3,12,17,33,81,105]; 2) the spinal cord (substantial gelatinosa), where the density of estrogen receptors changes with changes in estrogen levels over the menstrual cycle [6,7]; and 3) the brain where estrogen receptors are prevalent in regions (periaqueductal grey, thalamus, amygdala, and central grey) that modulate pain perception [81,97,99,104] (Fig. 2). Additionally, ovarian hormones may affect pain perception by modulating numerous neurotransmitters including: serotonin, dopamine, β-endorphins, and γ-amino-butyric acid (GABA) [54,66,91]. In fact, the interaction between estrogen and GABA has been shown to be one of the most important neurotransmitter interactions for pain modulation, with estrogens modulating GABA synthesis, release, and production, as well as upregulation of GABA receptors, and modulation of their binding affinity [3,54,91,98].

4. Literature search

We searched Medline, PubMed, and Google Scholar, as well as the references of papers that reviewed the relationship between the menstrual cycle, ovarian hormones, and pain. References of papers were searched in order to identify potentially relevant studies that might not have been retrieved by traditional subject searching. Results were limited to those in English. In order to capture as many studies as possible, the search was unlimited by any time interval. Search terms were *chronic pain*, *chronic non-cancer pain*, *migraine headache*, *temporomandibular joint disorder*, *irritable bowel syndrome*, *fibromyalgia*, *rheumatoid arthritis*, and *chronic pelvic pain*, each in turn crossed separately with *ovarian hormones/steroids*, *estrogen/progesterone*, *hormonal replacement therapy*, *oral contraceptives*, *menopause*, and *menstrual cycle*.

Focusing on CNCP conditions and their relation to hormonal changes, the search produced 385 papers (dates ranging from 1983-2012). We excluded any that were not clinical, leaving a total of 50 studies: 8 for MSP, 9 for migraine headache, 5 for TMD, and 28 for chronic pelvic pain (6 IBS and 22 randomized controlled trials [RCTs] testing the efficacy of hormone therapy in alleviating chronic pelvic pain due to endometriosis). For all these studies, patients were diagnosed with a CNCP condition and pain was assessed by at least one self-report measure. All studies recorded changes in pain severity either by: 1) querying current pain intensity (visual analogue scale, verbal rating scale, and/or McGill Pain Questionnaire); 2) inducing pressure pain to measure pain pressure threshold (PPT) by pressure dolorimetry; 3) using physiological changes such as grip strength, finger joint size, and rectal sensitivity, or stool softening. Most studies used the menstrual cycle as a proxy for the absolute levels of estrogens and progestagens. They counted backward or forward from the first day of menstruation, assuming an average cycle length of 28 days. Some

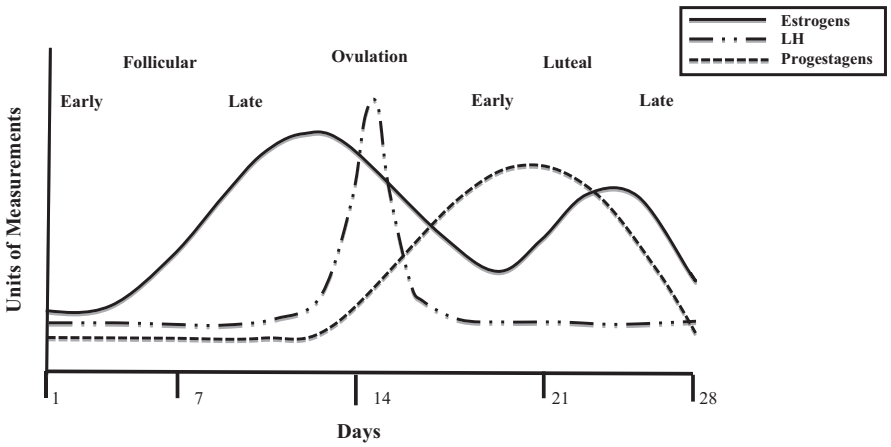

Fig. 1. Schematic of a 28-day menstrual cycle. LH, luteinizing hormone.

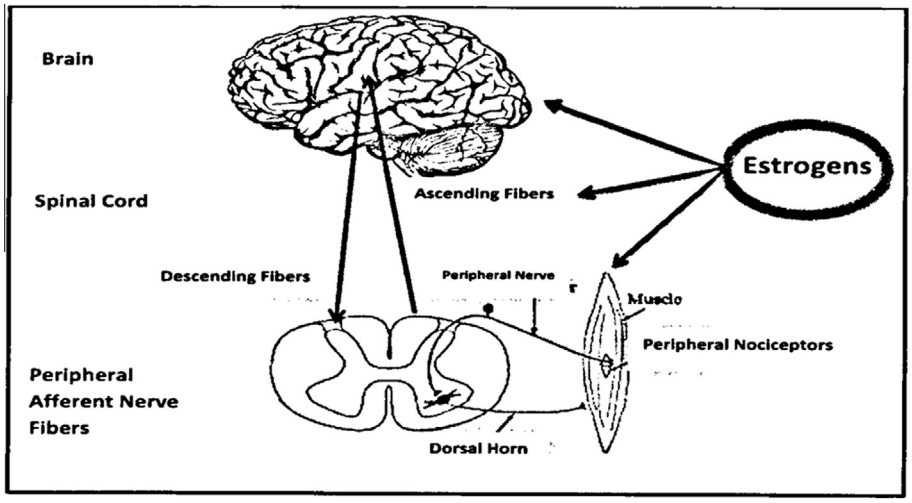

Fig. 2. Potential sites for ovarian hormonal modulation include the following: 1) peripheral afferent nerve fibres; 2) the spinal cord; 3) higher brain centers.

assumed hormone status based on other events in women's lives that modulate serum hormone levels: pregnancy and postpartum, pre- and menopausal periods, as well as the use of oral contraceptives (OC) and hormone replacement therapy. Only 3 studies measured hormonal status directly.

5. Musculoskeletal pain (MSP)

A total of 8 clinical studies were found that investigated the relationship between fibromyalgia or RA severity and the menstrual cycle (Table 1).

5.1. Fibromyalgia

Fibromyalgia is one of many CNCP conditions that tend to occur predominately in women and more frequently during reproductive ages [75].

A total of 5 studies investigated fibromyalgia pain severity in relation to the menstrual cycle and/or pregnancy, abortion, and menopause [4,8,75,77,80].

Two studies compared premenopausal to menopausal participants and reported that menopausal participants had higher pain scores than premenopausal [8,80]. A study of 26 participants compared fibromyalgia pain severity among 4 groups of women with different ovarian hormone levels: those who were pregnant, those who underwent abortion, those who were cycling, and those taking OC. They found that the last trimester of pregnancy was correlated with the highest pain scores. Additionally, in regularly cycling participants, more fibromyalgia pain was reported in the premenstrual than postmenstrual phase. In contrast, there were no changes in pain severity in women using OC or following abortion [77].

While self-reports were used by all studies for recording changes in symptom severity, 2 studies tested changes in PPT using pressure pain testing [4,8] and one study used ischemic pain testing [75], while the rest of the studies used only self-reports [77–80]. Despite these discrepancies, 3 studies out of the total 5 were consistent in finding an increase in pain severity during phases when estrogen levels were low [8,77,80]. In contrast, the other 2 studies, one of which used daily urine measurements for ovarian hormones, reported no changes in pain scores across the menstrual cycle [4,75].

In sum, while opposing evidence exists, the weight of the evidence suggests the idea that fibromyalgia pain symptoms are greatest during the menstrual cycle when estrogens are low.

5.2. Rheumatoid arthritis (RA)

RA is an immune system disease characterized by inflammation, morning stiffness, and chronic pain [61]. Since ovarian hormones have been considered as antiinflammatory agents, researchers have studied the impact of ovarian hormones on the severity of RA.

Two studies compared variation in pain sensitivity across the menstrual cycle in cycling women with RA [61,89]. While both studies used self-report questionnaires, Rudge and colleagues [89] used additional objective measurements (finger joint size, grip strength, and body weight). Both studies found that the severity of RA pain varies with the phases of the menstrual cycle, although there was no consensus on which menstrual phase correlates with greater pain symptoms. Latman [61] reported less joint pain and morning stiffness during the luteal phase, which, in his schema, was a phase when estrogen and progesterone plasma levels are high. In contrast, Rudge and colleagues [89] found a decrease in grip strength during menses and an increase in the joint size in the first 6 days after menses compared with other time periods of the menstrual cycle, which were considered to reflect low estrogen phase.

5.3. Chronic back, neck, ankle, and knee pain

Only one study investigated how MSP in various areas (eg, neck, shoulder, back, joints) varied with hormone status [43]. This study found that pain severity was greater during premenstrual and menstrual phases compared with mid-menstrual and ovulatory phases, suggesting that pain sensitivity was greatest when levels of estrogens were lowest.

Hence, we can conclude that, according to the majority of MSP studies, MSP symptoms vary over the course of the menstrual cycle, with periods of low estrogen (ie, menopause, early follicular and late luteal phase) being when pain is the greatest [8,43,61,77,80,89].

6. Migraine

The finding that nearly half of all women who are diagnosed with migraine headache are actually within their reproductive age suggests that fluctuations of ovarian hormones occurring during the reproductive years may play a role in modulating these painful attacks [65,100]. In fact, some migraine headaches have long been recognized to be in sync with different phases of the menstrual cycle. Thus, migraine headaches have been subdivided based on

Table 1
Clinical studies investigating the relationship between MSP and phases of the menstrual cycle.

Author(s)	CNCP Condition	Comparative participants	Participants blinded (Y/N)	Menstrual cycle	Methodology	Results
Ostensen et al., 1997 [77]	Fibromyalgia	- 26 female patients	N	Self-report	Retrospective self-report of pain severity changes during pregnancy/ abortion/use of OC/breastfeeding	- More pain during last trimester in pregnancy - More pain in 72% premenstrual - No changes in pain among women using OC, or during abortion
Anderberg et al., 1999 [8]	Fibromyalgia	- 17 premenopausal with FM - 18 menopausal with FM - 13 postmenopausal controls	N	Self-report	- Self-report questionnaires - Daily pain intensity ratings - PPT (algometer)	- More pain among postmenopausal than premenopausal patients - More pain in - perimenstrum vs ovulatory phase among premenopausal
Alonso et al., 2004 [4]	Fibromyalgia/RA	Fibromyalgia RA healthy controls	N	Self-report	Using dolorimetry tender point palpation and self-reported pain diaries	No significant differences in pain severity or number of tender points between the follicular and luteal phases
Pamuk & Cakir, 2005 [80]	Fibromyalgia	- 80 premenopausal - 72 postmenopausal with FM	N	Self-report	- VAS - Self-report questionnaires	- More pain among menopausal - More pain and fatigue - in menstrual, luteal phases vs other phases among premenopause
Okifuji & Turk, 2006 [75]	Fibromyalgia	- 74 cycling with FM - 74 cycling controls	N	Blood sampling for 9 days to measure ovulation	- Tender point palpation - Grip strength testing - Ischemic pan threshold and tolerance testing	- No difference in pain across phases - Lower pain threshold & tolerance in patients
Latman, 1983 [61]	RA	- 14 cycling with RA	Y	Self-report	- Self-report questionnaires	- Less joint pain, morning stiffness during luteal phase vs early follicular phase
Rudge et al., 1983 [89]	RA	- 7 cycling with RA - 6 cycling controls	N	Self-report	- Daily finger joint size, grip strength, body weight measurements	- Decrease in grip strength & increase in joint size during menses
Hellstrom & Anderberg, 2003 [43]	Chronic back, neck, ankle, knee pain; fibromyalgia	- 20 cycling with chronic pain	Y	Self-report	- Self-report questionnaire	- More pain during premenstrual and menstrual phases than mid-menstrual and ovulatory phases

FM, fibromyalgia; OC, oral contraceptives; PPT, pain pressure threshold; RA, rheumatoid arthritis; VAS, visual analogue scale.

Table 2
Clinical studies investigating the effect of the menstrual cycle on the severity of migraine headache.

Author(s)	CNCP Condition	Comparative Participants	Participants blinded (Y/N)	Menstrual cycle	Methodology	Results
MacGregor & Hackshaw, 2004 [65]	Migraine without classification	- 155 cycling patients	N	Self-report	- Self-report questionnaire	- More pain during perimenstrum
Martin et al., 2005 [68]	Migraine without classification	- 21 cycling patients	N	Daily urine samples	- Self-report questionnaire	- More attacks during menses than during mid-cycle
MacGregor et al., 1990 [64]	Menstrual MigraineAttacks	- 55 cycling patients	N	Self-report	- Self-report questionnaire	- 4 patients had MM without aura - 19 patients had MM + attacks throughout the cycle - 18 patients had attacks throughout the cycle - 14 patients had no MM attacks
Varlibas & Erdemoglu, 2009 [110]	Menstrual migraine attacks	- 31 cycling patients - 22 healthy controls	N	Self-report	- Electromyography from stimulation of trigeminal nerve	- More brainstem excitability during premenstrual and follicular phase among patients
Granella et al., 2004 [38]	Menstrual migraine attacks	- 64 cycling patients	N	Self-report	- Self-report questionnaire	- MM attacks are more severe, longer in duration, and have greater work-related disability than nonmenstrual attacks
Johannes et al., 1995 [51]	Migraine classified by headache features	- 74 cycling patients	N	Self-report	- Self-report questionnaire	- More MO during first 3 days of menstruation
Cupini et al.,1995 [23]	Migraine classified by headache features	- 232 cycling - 268 menarche - 156 pregnant - 122 using OC - 36 menopausal patients	N	Self-report	- Self-report questionnaire	- More MO attacks during menses - More MA during pregnancy - No difference in menarche, on OC, menopause
Stewart et al., 2000 [100]	Migraine classified by headache features	- 81 cycling patients	N	Self-report	- Self-report questionnaire	- More MO attacks perimenstrually
Mattsson, 2003 [71]	Migraine classified by headache features	- 728 cycling patients	N	Self-report	- Self-report questionnaire	- 21% of women suffer from MO - 2% only suffer from MA - 75% of the attacks were exacerbated during perimenstrum

MA, migraines with aura; MM, menstrual migraines; MO, migraines without aura; OC, oral contraceptives.
Note: Since across the 9 studies there was a great variability in terms of study design and migraine terminology, we grouped the 9 studies according to the way the studies themselves classified them.

both headache features and according to whether or not the attacks occur just prior to and during menses [38,64,110]. Explicitly recognizing the role of ovarian hormones has led to the suggestion that exogenous hormones might be used successfully as treatment [64]. We found a total of 9 studies investigating the role of ovarian hormones on migraine headache (Table 2).

6.1. Migraine (without further classifications)

Two studies investigated the relation between the menstrual cycle and migraine attacks by looking at prevalence and severity [65,68]. While both studies used self-reported questionnaires to record pain severity changes over the course of 3 menstrual cycles, each study used different methods to identify the different phases of menstrual cycle. MacGregor and Hackshaw [65] used daily diaries. Martin and his colleagues [68] collected daily urine samples to evaluate hormonal levels directly and used these levels to identify different phases of the menstrual cycle. Both studies found that migraine attacks were more prevalent 2 days before and 2 days after menses; and that those attacks – menstrual related – tended to be more severe than other attacks occurring at other times of the cycle.

6.2. Menstrual migraine attacks (MM)

Three studies divided migraine attacks into those that occurred specifically around menstruation, called menstrual migraine (MM), and those occurring at other phases of the menstrual cycle (non-MM) [38,64,110].

Two of these studies compared the prevalence of MM with non-MM attacks [38,64]. Among women in their reproductive years, MM had a higher prevalence and were more severe, longer in duration, associated with significantly greater work-related disability, and less responsive to nonhormonal treatment (β-blockers, calcium antagonists, antidepressant medication, antiepileptic drugs, etc.) than other attacks not occurring perimenstrually [38,64]. Using a variety of methods including epidemiological, comparison of hormonal to nonhormonal treatments, and electrophysiological, these studies support the idea that there are types of migraine headache specifically related to the menstrual cycle phase (MM). While MM may be only a subset of migraine headache type that is associated with ovarian hormones, for this subtype the indication is that ovarian hormones play a role in this type of migraine. Further controlled studies looking at the effectiveness of hormonal treatments for MM are needed to test this hypothesis [38].

The third study measured pain severity by brainstem excitability in women with MM, comparing MM patients and healthy controls [110]. There was no statistically significant difference in excitability at any phase of the menstrual cycle in controls. However, in women with MM, brainstem excitability varied significantly depending on whether it was measured in the perimenstrum or the follicular phase. In these women, brainstem excitability was significantly greater during the follicular period (headache free) than during the perimenstrum (headache period).

Taken together, these studies suggest that low estrogen is associated with a subset of migraine attacks.

6.3. Migraine classified by headache features

Four studies investigated whether the following types of migraine attack vary with hormonal status: migraine without aura (MO), migraine with aura (MA), tension-type, and all other migraine headaches [23,51,71,100].

All 4 found that MO was significantly elevated during the first 3 days of menstruation, and risk for MA was not significantly increased either during the 2 days immediately preceding menses or on the estimated day of ovulation. One study reported that MA was more prominent during pregnancy [23]. In contrast, no significant difference between MO and MA was found at menarche, among women using OC, or among menopausal women. Taken together, all studies on the different types of migraine support the idea that ovarian hormones mediate migraine headache characteristics – especially migraine headache without aura, which is more prevalent among cycling women – and that the symptoms tend to vary with changing estrogen levels. Further supporting the idea that it is changing hormone levels rather than absolute levels, are the studies using participants for whom estrogen levels are not fluctuating, as is the case in pregnant women or women using OC. In those studies in which estrogen levels are kept constant, the frequency and intensity of the headaches dissipate [23], providing strong evidence that ovarian hormones, levels, and fluctuation affect migraine headache pain.

7. Temporomandibular disorder (TMD)

Many epidemiological studies have reported that the prevalence of TMD is higher among women and highest during the reproductive years [62]. Moreover, the age of onset is almost always after menarche, raising the question of whether ovarian hormones or hormonal fluctuations play a role in modulating TMD. In our review we identified a total of 5 clinical studies investigating the relation between TMD and ovarian hormones (Table 3).

Three studies investigated variations in pain severity across the menstrual cycle, comparing regularly cycling patients to those using OC [24,62,96]. One study determined different phases of the menstrual cycle using ovulation kits [62], while the other 2 used daily diaries. In regularly cycling women, all studies reported variations in daily pain severity ratings, with pain levels reaching their maximum during menses and at the mid-luteal phase. Comparisons with women on OC were less consistent across studies. One found greater variability in pain severity among naturally cycling patients as compared to those on OC, suggesting that pain thresholds and severity stabilize when one minimizes the effect of hormonal fluctuations [24]. Another study reported that there was more pain during menstruation for both normally cycling and women on OC, suggesting that lower levels of estrogens are still affecting pain severity [62].

In a study that used PPT to determine changes in experimentally induced pain sensitivity, PPT was highest during the follicular and luteal phases and lowest during perimenstrum [49], supporting the conclusion that pain is greatest when estrogen levels are lowest.

A study evaluating the effect of hormone replacement therapy (HRT) on TMD pain in menopausal women found that those receiving HRT experienced higher TMD pain intensity than those not receiving HRT, suggesting that there may be differences between endogenous and exogenous hormonal effects on chronic pain conditions [122].

Taken together, these studies demonstrate a TMD pain pattern similar to that of other CNCP conditions; sensitivity to pain varies across the menstrual cycle, with lowest thresholds and greatest sensitivity when estrogen levels are low.

8. Chronic pelvic pain

Chronic pelvic pain, like the other CNCP conditions, is more prevalent among in women in their reproductive years [36]. However, correlating menstrual cycle phase and chronic pelvic pain has been contentious, in part because of how it is defined. Some choose to define it as "*noncyclic pain of at least six months duration, localized to the pelvis, anterior abdominal wall, at or below the umbilicus and lower back and buttocks*" [59,84], and another as "*continuous or intermittent pain in the lower abdomen, lasting for at least 6 months and not exclusively related to menstrual period or sexual intercourse*" [117,121]. That said, some causes of chronic pelvic pain are acknowledged as hormonally driven, for example, endometriosis, making it difficult to not consider the role of hormones. Furthermore, there is a considerable overlap among conditions that might cause chronic pelvic pain (eg, endometriosis, interstitial cystitis, and IBS), making it difficult to definitely identify any one of them as causative [116].

There were 28 clinical studies (6 for IBS, and 22 RCTs for chronic pelvic pain due to endometriosis) that investigated the relationship between chronic pelvic pain and ovarian hormones.

8.1. Irritable bowel syndrome (IBS)

IBS is a common nongynecological cause of chronic pelvic pain and may account for up to 60% of the referrals [70,113]. IBS is characterized by changes in bowel habits and increased visceral sensitivity. Women with IBS experience more frequent and looser stools, as well as abdominal cramping and distension close to menses, suggesting a possible relation between IBS symptoms and the menstrual cycle [18,45].

Six clinical studies of women with IBS investigated changes in gastrointestinal symptoms (bowel discomfort, abdominal pain, bloating, and alteration in bowel movements) across the different phases of the menstrual cycle (Table 4).

Of these, 3 reported variations in gastrointestinal symptoms, including altered motility and/or enhanced perception of gastrointestinal symptoms (eg, bloating, distension) and rectal sensitivity (as measured by rectal response to balloon distension in women with IBS) [18,42,45]. Two of these studies consistently reported more abdominal pain and bloating during menses as compared with all other phases of the menstrual cycle [18,45]. Two studies compared changes in severity between Crohn disease and ulcerative colitis, and IBS across the menstrual cycle; both of these studies found that patients had more abdominal pain during the premenstrual phase than did the controls [16,53]. However, 2 studies, one that measured hormones directly (in plasma) [42] and another that used self-report [5], found no difference in IBS pain across menstrual phases.

Thus, as with other studies of CNCP, although there are conflicting results, the weight of the evidence suggests a role for ovarian hormones in modulating abdominal symptoms, which generally are worse in the perimenstrual phase, a time during which estrogen levels are low.

8.2. Endometriosis

Endometriosis, thought to be responsible for one-third of the probable causes of chronic pelvic pain, is found almost exclusively in menstruating women of reproductive age [34]. Endometriosis is

Table 3
Clinical studies investigating the relation between TMD and the menstrual cycle.

Author(s)	CNCP condition	Comparative participants	Participants blinded (Y/N)	Menstrual cycle	Methodology	Results
Dao et al., 1998 [24]	TMD	- 7 cycling patients - 5 using OC patients	Y	Self-report	- Self-report questionnaire - VAS	- Greater variability in pain severity among cycling patients than patients using OC
Wise et al., 2000 [122]	TMD	- 34 menopausal patients not using HRT - 53 menopausal patients using HRT	N	Self-report	- MPQ - Self-report questionnaire for pain intensity ratings	- More pain for HRT group
Isselee et al., 2002 [49]	TMD	- 10 cycling patients	N	Self-report	- VAS - PPT (pressure algometry) - McGill Pain Questionnaire	- PPT highest during follicular and luteal phases, lowest during perimenstrum
LeResche et al., 2003 [62]	TMD	- 35 cycling patients - 35 patients on OC - 35 cycling controls - 21 males patients	N	Ovulation kit	- Self-report questionnaire for pain	- More pain during menstruation for cycling and those using OC
Sherman et al., 2005 [96]	TMD	- 18 cycling patients - 25 patients on OC - 25 cycling controls - 26 controls on OC	N	Self-report	- PPT (algometer) - Ischemic arm pain task	- More pain at menses, mid-luteal phase in cycling women with TMD - More pain during late luteal phase among women with TMD on OC

HRT, hormonal replacement therapy; MPQ, McGill Pain Questionnaire; OC, oral contraceptives; PPT, pain pressure threshold; TMD, temporomandibular joint disorder; VAS, visual analogue scale.

Table 4
Clinical studies investigating changes in IBS across the menstrual cycle.

Author(s)	CNCP condition	Comparative participants	Participants blinded (Y/N)	Menstrual cycle	Methodology	Results
Kane et al., 1998 [53]	IBS	- 49 cycling with UC - 49 cycling with CD - 46 cycling with IBS - 90 cycling controls	Y	Retrospective self-report	- Self-report on variations in symptoms across menstrual cycle	- More abdominal symptoms during pre and menstrual phases
Chang et al., 2001 [18]	IBS	- 77 female with bloating - 303 female patients with bloating and distension	N	Self-report	- VAS - Self-report questionnaire on bowel symptoms	- 40% of females with bloating during menses - 43% of females with bloating and distension related to menses
Houghton et al., 2002 [45]	IBS	- 29 cycling with IBS	N	Self-report	- Rectal response to balloon distension - Self-report questionnaire	- More abdominal pain and bloating during menses
Heitkemper et al., 2003 [42]	IBS	- 93 cycling with IBS - 56 using OC with IBS - 35 cycling control - 7 using OC control	N	Blood sample during mid-luteal phase, ovulation kit	- Self-report questionnaire	- No difference in pain across phases - More pain among IBS patients than controls
Altman et al., 2006 [5]	IBS	- 38 with dysmenorrhea & PMDS & IBS - 59 with PMDS & IBS - 15 with dysmenorrhea & IBS - 114 with IBS only	N	Self-report	- Self-report questionnaire	- No difference in pain across phases
Bernstein et al., 2012 [16]	IBS	- 151 premenopausal with CD - 87 premenopausal with UC - 156 premenopausal controls	N	Retrospective self-report	- Self-report questionnaire	- More pain during premenstrum

IBS, irritable bowel syndrome; OC, oral contraceptives; PMDS, premenstrual dysphoric syndrome; UC, ulcerative colitis; CD, Crohn disease; VAS, visual analogue scale.

not reported before menarche and generally disappears with menopause (unless women are taking HRT) [56]. Endometriosis is known to be an estrogen-dependent condition, with estrogens directly stimulating growth and influencing the proliferation of the ectopic endometrial tissue [2,34,36,47,112,113]. In about 70% of patients with endometriosis, hormone treatments (eg, OC, GnRH analogues, progestins, and danazol [an androgen agonist]) have been used successfully to alleviate chronic pelvic pain [37,40,48,55,59,74,76,101]. It is well known that endometriosis waxes and wanes with ovarian hormone levels [34]. However, as noted above, at least one definition of chronic pelvic pain excludes any relation of pain to the menstrual cycle. Perhaps reflecting the impact of this definition, we were not able to identify any studies of how the chronic pelvic pain associated with endometriosis might vary with changes in hormones across the menstrual cycle.

Found instead were 22 RCTs testing the efficacy of hormone therapy in alleviating chronic pelvic pain due to endometriosis (Table 5). From among these 22, 7 compared hormone therapy to placebo [13,27,30,41,63,78,102]. One evaluated the efficacy of OC in comparison to placebo for patients diagnosed with chronic pelvic pain associated with endometriosis [41]; 4 studies performed RCTs to investigate the efficacy of a GnRH agonist vs placebo

Table 5
Randomized controlled trials investigating the efficacy of hormonal treatment in treating CPP associated with endometriosis.

Author(s)	Treatment groups	# of Participants	Pain scale	Results
Harada et al., 2008 [41]	OC vs placebo	- 51 OC - 49 placebo	- VRS - VAS	- Reduce pain in OC group
Dlugi et al., 1990 [27]	LA vs placebo	- 26 LA - 26 placebo	- VAS	- More pain relief for GnRH group
Fedele et al., 1993 [30]	Buserelin acetate vs placebo	- 16 placebo - 19 buserelin acetate	Analogue & multidimensional	- More pain relief for GnRH group
Bergqvist et al., 1998 [13]	Triptorelin vs placebo	- 24 triptorelin - 25 placebo	- VAS	- More pain relief for GnRH group
Ling, 1999 [63]	LA vs placebo	- 46 placebo - 49 LA	- VAS	- More pain relief for GnRH group
Vercellini et al. 1993 [114]	OCs vs goserelin	- 29 goserelin - 28 OCs	- VAS - VRS	- Pain scores reduced for both groups
Guzick et al., 2011 [40]	OCs vs LA	- 26 OCs - 28 LA	- VAS	- No significant differences between groups
Henzl et al., 1988 [44]	Nafarelin vs danazol	- 213	- VAS	- Reduction in both groups GnRH analogues fewer side effects
Wheeler et al. 1992 [119]	LA vs danazol	- 270	- VAS	- Reduction in both groups
Crosignani et al., 1992 [22]	LA vs danazol	- 67	- VAS	- Pain reduced in both groups
Adamson et al., 1994 [1]	Nafarelin vs danazol	- 213	- VAS	- Both treatments provided significant relief
Cirkel et al., 1995 [19]	Triptorelin vs danazol	- 30 triptorelin - 25 danazol	- VAS	- Dysmenorrhea treated successfully by both
Petta et al., 2005 [82]	LNG-IUS vs depot GnRH analogue	- 39 LNG-IUS - 43 GNRH analogue	- VAS	- Significant decrease in CPP in both groups
Bayoglu Tekin et al. 2011 [10]	Mirena vs Zoladex	- 20 Mirena - 20 Zoladex	- VAS - TESP	- GnRH analogue led to significant decrease in both VAS & TESP scores
Overton et al., 1994 [78]	Dydrogesterone vs placebo	- 62	- VAS - PRs	- Pain scores were reduced significantly for the dydrogesterone group
Strowitzki, Faustmann, et al., 2010 [102]	Dienogest vs placebo	- 96 placebo - 102 dienogest	- VAS	- Dienogest is significantly more effective than placebo for treating endometriosis-associated CPP
Strowitzki, Marr, et al., 2010 [103]	Dienogest vs LA	- 124 dienogest - 128 LA	- VAS	- Dienogest has equivalent efficacy to depot LA in relieving the pain of endometriosis
Telimaa, Puolakka, et al., 1987 [106]	MPA vs danazol vs placebo	- 18 danazol - 16 MPA - 17 placebo	- VAS	- Significant relief from both danazol and MPA
Telimaa, Ronnberg, et al., 1987 [107]	MPA vs danazol vs placebo	- 17 MPA - 18 danazol - 16 placebo	- VAS	- Significant reduction of pain by both danazol and a high dose MPA treatment
Fedele et al., 1989 [29]	MPA vs danazol	- 11 MPA - 12 danazol	- VAS and analogue scale	- Pain was relieved in both groups, however, dysmenorrhea recurred in 66% of the MPA group and 58% of the danazol group
Vercellini et al., 1996 [111]	MPA vs OC + danazol	- 40 MPA - 40 danazol/OC	- VAS - VRS	- More pain relief in MPA group - Dysmenorrhea scores significantly greater in the OC/danazol group
Vercellini et al., 2013 [112]	Progestins vs surgery	- 51 surgery - 103 progestins	- VAS	- Both equally effective in pain relief

CPP, chronic pelvic pain; GNRH, gonadotropin releasing hormone; LA, leuprolide acetate; LNG-IUS, levonorgestrel-releasing intrauterine system; MPA, medroxyprogesterone acetate; OC, oral contraceptives; TESP, total endometriosis severity profile; VAS, visual analogue scale; VRS, verbal rating scale.

[13,27,30,63], and 2 studies compared progestin to placebo [78,102]. In each of these studies, pain scores were reduced significantly during all hormonal treatment, compared to placebo.

Fourteen of the 22 RCTs compared the efficacy of one type of hormone therapy with that of another type of hormone therapy [1,10,19,22,29,40,44,82,103,106,107,111,114,119]. Two studies compared the relative efficacy of GnRH analogues and OC [40,114]. Five compared GnRH analogues with danazol [1,19,22,44,119]. Two compared GnRH analogues with levonorgestrel-releasing intrauterine system [10,82]. One investigated the efficacy of GnRH analogue with dienogest [103]. Four studies compared danazol and progestins [29,106,107,111], 2 of which also compared both drugs to placebo [29,106], and one of which compared danazol combined with OC to progestins [111]. Results revealed that all hormonal therapies were effective in reducing chronic pelvic pain and no one hormonal therapy was better than any other.

Finally, one study compared hormonal treatment to surgeries that remove the ectopic patches of endometriosis like laparoscopy and hysterectomy. This study found that both treatments were equally effective in alleviating chronic pelvic pain associated with endometriosis after a 12-month follow-up [112].

All of these studies demonstrated that hormone therapies can provide relief from chronic pelvic pain, with no one hormonal treatment being significantly more effective than another [76]. This supports the idea that endometriosis, one of the main causes of chronic pelvic pain, may be hormonally driven, thus also linking this pain condition with ovarian hormones. Indeed, based on this, some advocate for the importance of identifying any temporal patterns or cyclicity in the assessment of chronic pelvic pain [47,115].

9. Summary and implications of the literature

In reviewing clinical studies that investigated the relation between the severity of CNCP and any events associated with changes in the levels of ovarian hormones, we found only 50 clinical studies spanning 3 decades across 4 CNCP conditions: MSP, migraine, TMD, and chronic pelvic pain. This is a surprising paucity

of studies given that we placed no time constraint on our search, women are overrepresented in CNCP conditions, and there have been considerable advances in the understanding of how ovarian hormones can affect pain perception.

We also found literature that included different methods and interpretations of phases of the menstrual cycle. In spite of this, there was a consensus among the studies that pain severity varies during the different phases of the menstrual cycle in women with CNCP conditions (Fig. 3). In most studies, participants' self-reports revealed increased pain severity at times that were defined by investigators as low estrogen. Taken together, these studies strongly suggest that a low estrogen milieu exacerbates the severity of CNCP. However, this point of consensus emerged from studies using different approaches and methodologies.

Since different CNCP conditions have different characteristics, it was not surprising that pain was measured differently across CNCP conditions. For example, migraines are characterized as "attacks" and time-limited, while fibromyalgia is characterized by constant pain that might wax and wane, but usually never goes away. These might require different approaches. However, even when investigators were studying the same CNCP condition, methods varied. Some studies queried the simple presence of pain while others, the changes in pain severity, or occurrences over a fixed time period. In addition to self-reports, a few studies used objective pain measurements [4,8,75]. This variation in approaches—even for a given condition—limits the ability to perform a meta-analysis that could provide valuable evidence on which treatment decisions could be made.

Among these 50 studies, both participants and control groups also varied, making comparison across studies difficult. Three studies compared women with CNCP of reproductive age with menopausal women [8,23,80]. Five compared cycling women with CNCP to those on OC [23,24,42,62,96]. Others compared women with CNCP conditions to women without CNCP. Twenty-two were RCTs and gave hormones or placebo to women with the same CNCP (see Table 5).

All studies used the menstrual cycle as a proxy for the ovarian hormone levels, therefore, all used self-reports to identify the different phases of the menstrual cycle, assuming that each phase reflected the actual hormonal levels or changes in hormone levels. Only 4 studies confirmed hormone levels or stage of menstrual cycle by direct measures using blood [42,75], daily urine samples [68], or ovulation kits [62]. It is well established that there are individual differences in hormone levels across cycles as well as in cycle length, both within and between women [68]. Thus, the results of studies that do not measure hormones directly cannot be certain as to both absolute hormone levels and menstrual cycle phase, with its coincident variation in hormone levels [11,39,60]. This lack of clarity likely contributes to the inconclusive results of a number of the studies reported [15], as well as to our not knowing whether it is absolute or varying hormone levels that influence pain reports.

The resulting inconsistencies between studies in the interpretations of the different phases of the menstrual cycle in relation to ovarian hormone levels contribute to difficulties comparing studies. For example, Pamuk and Cakir [80] reported MSP symptoms increase during the luteal phase; Latman [61] reported increase in the follicular phase. However, both concluded that pain increases were due to low estrogen levels. In fact, both the luteal and follicular phases contain sub-phases when estrogens and progestagens are both high and low because hormone levels vary continuously (Fig. 1). The early luteal phase is characterized by high levels of estrogen, while late luteal is characterized by low levels. Given this, it is not possible to know what hormone levels are simply by designating cycle phases.

As well, when menstrual cycle is used as a proxy for hormone levels, it is difficult to obscure the menstrual cycle focus of the study. Only 4 out of 50 studies were carried out with participants blinded to the hypothesis that chronic pain is related to menstrual cycle [24,43,53,61]. A focus on the menstrual cycle itself carries negative connotations. Research has shown that being aware of a research study's menstrual focus may affect self-reported negative symptoms [57,69,123]. As demonstrated in a review of the literature on mood and the menstrual cycle, when the menstrual cycle focus of the study was not obscured, negative mood was often correlated with phases of the cycle, while in the studies in which the menstrual cycle focus of the study was obscured, association of the premenstrual phases of the cycle with negative mood was unusual [87]. In a study of daily mood measured across 3 full menstrual cycles in community dwelling, non-help-seeking women in whom the menstrual cycle focus of the study was obscured, neither positive nor negative mood were correlated with menstrual cycle phase [88]. When hormones were measured daily for 42 days in a subset of these women, there was no correlation between either estrogens or progestagen levels with either positive or negative mood [95]. In fact, the 2 strongest correlations with mood in both these studies were psychosocial factors: perceived stress and health [88,95]. Given the menstrual cycle's negative cultural overlays unless the menstrual cycle focus of the study is obscured, it will be difficult to separate negative attitudes toward menstruation and pain perception.

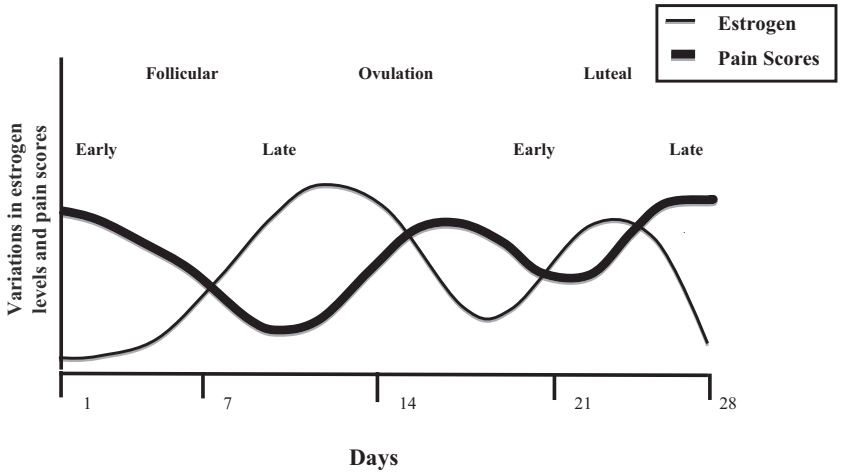

Fig. 3. Schematic summarizing changes in the levels of pain severity and estrogens over a typical menstrual cycle based on the literature reviewed.

Two CNCP conditions stood out, showing strong correlation of pain with the menstrual cycle: migraine and endometriosis. For these conditions there was good evidence of menstrual cyclicity to the pain, strengthening the link between increased pain symptoms and ovarian hormones. With respect to migraine, a specific type of migraine that was sensitive to ovarian hormones, MM, was identified and suggested to be differentiated in treatment from other types [38,64,110]. Moreover, the symptoms of migraines occurring perimenstrually were differentiated from those that occur sporadically; MM occurred without an aura, and nonmenstrual migraines with an aura, suggesting different underlying neural circuits. With respect to chronic pelvic pain (CPP) due to endometriosis, numerous RCTs have tested hormone treatments with therapeutic success; one determined that hormone therapy is as efficacious in relieving pain as surgery, raising an important question about the relative benefits of surgery [63]. Understanding hormonal involvement in endometriosis has been important in establishing a clinical pathway of noninvasive diagnostic tests, followed by a trial of hormone therapy with GnRH agonists, rather than laparoscopy [46,63]. The emergence of this clinical pathway underscores the potential value of considering the role of ovarian hormones in modulating CNCP.

With the exception of studies on hormonal treatments for endometriosis, no studies controlled for the current treatments that participants might be undergoing. This seems like a serious oversight because it has been reported that ovarian hormones might modulate pain medications, especially opioids, affecting potency, efficacy, and selectivity [20,21]. Some opioids are less effective in women than others [20,32,35,92,93].

Except for an acknowledgement that endometriosis often overlaps with IBS, none of the 50 studies controlled for other CNCP conditions. This is surprising since it is well known that CNCP rarely occurs as separate conditions [26,72,86,124]. In fact, it may be more appropriate to think of chronic pain as a constellation of conditions. Dao and colleagues [25] found that 70% of fibromyalgia patients reported orofacial pain. Based on this, Klineberg et al. [58] suggested that fibromyalgia (generalized) and orofacial (localized) pain might be variations of a similar problem. CPP has been reported to overlap with other CNCP conditions [116]. Many studies point out that it is, in fact, this overlapping of pain conditions that makes it difficult to adequately treat chronic pain conditions [52,83,115]. For some types of CNCP, the occurrence of one pain condition might serve to mitigate pain sensation of another pain condition via descending noxious inhibitory control [108]. For others, the co-occurrence of one pain condition sensitive to ovarian steroids with another that is not might mask the sensitivity of the one that is [15]. Thus, failure to take co-occurring conditions into account is an important omission.

It is worth considering, with respect to periodicity of pain related to the menstrual cycle, that there might be the co-incidence of CNCP conditions that themselves are affected by ovarian hormones such as: cyclic CPP (for example: endometriosis, IBS, migraine) [118]. Other co-occurring conditions influenced by ovarian hormones, such as premenstrual dysphoric disorder (PMDD), may also influence CNCP; women with PMDD have higher ischemic pain sensitivity than controls during menses [32] and are more vulnerable to TMD [62]. With this in mind, it is possible that underlying cyclic CPP or other cyclic conditions such as PMDD are responsible for the noted variations of pain severity across the menstrual cycle. Taking these multiple conditions into account might prove fruitful to better understanding how to treat CNCP in women.

In spite of the growing consensus about the role of hormones in modulating CNCP, the question remains: Is it the absolute levels or fluctuation in hormones that affect pain severity? In their interpretation of their results, most studies have concluded that it was the level of hormones that mattered (eg, [8,80]). However, some studies have suggested that fluctuations in hormonal levels across the menstrual cycle are important in explaining pain severity (eg, [23,24,77]). For example, several studies reported an increase in pain intensity during menopause, early follicular, and late luteal phases, supporting the low estrogen hypothesis. Others found no variation in pain severity scores for participants using OC and/or treatments that abolished hormonal fluctuations, supporting the hormonal variation hypothesis. Ancillary to this question is: is it the absolute level or variations in the levels of estrogens alone or both estrogens and progestagens? None of the studies, except one [68], reported on the role of progestagens. Thus, we don't know what role, if any, progestagens or the relative level of progestagens/estrogens plays. It is worth noting that, as a group, these studies involve numerous pain conditions, which may vary in how they are affected by hormones, and which hormones. Thus, while the weight of the evidence supports some role of ovarian steroids in modulating CNCP in women, there are still many questions as to how important they are, for which conditions, and the dynamics of how they modulate pain – sensation and experience.

10. Recommendations

The literature reviewed strongly supports the notion that ovarian hormones play a role in modulating CNCP conditions. However, the aforementioned limitations, variations, and discrepancies in methodologies impede a definitive understanding for most conditions except MM and endometriosis. It may be that these inconsistencies and the resulting lack of clarity have contributed to the failure of hormonal effects being translated into medical practice for treatment of CNCP conditions. Based on extant studies as well as their gaps, we have outlined recommendations that we hope will help provide solid evidence of the impact of ovarian hormones on CNCP conditions:

1. Use a standardized study design using standard pain measurements;
2. Measure hormones daily and directly to accurately correlate both the continuously varying stages of the menstrual cycle and hormone levels with pain threshold, intensity, and symptomatology;
3. Obscure any menstrual cycle focus of the study;
4. Account for the effects of co-existing pain conditions, CPP in particular;
5. Consider any treatment and type of treatments in the analysis and interpretation of the data;
6. Include measures of other daily events both psychosocial and physiological to better understand how the effects of ovarian hormones interact with mood, stress, and social support on pain perception and experience.

Such studies will provide the evidence necessary to adequately discern whether or not and how CNCP is correlated with ovarian hormones. This, in turn, will open the way for determining how treatment efficacy might also depend on ovarian hormones ultimately to devise effective CNCP management for women.

Conflict of interest

There are no conflicts of interest to declare.

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