

**THE IMPACT OF PRIMARY DYSMENORRHOEA ON PAIN PERCEPTION,
QUALITY OF LIFE, AND SLEEP IN YOUNG HEALTHY WOMEN.**

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A thesis submitted to the Faculty of Science, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Doctor of Philosophy.

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DECLARATION

I declare that the work contained in this thesis is my own, unless otherwise specified. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. The work herein has not been submitted before for any degree or examination in any other university.

Signed on the _____ day of _____, 2014

RESEARCH OUTPUTS

Peer-reviewed publications

1. Iacovides S, Baker FC, Avidon I, Bentley A. Women with dysmenorrhoea are hypersensitive to experimental deep muscle pain across the menstrual cycle. *Journal of Pain* 14; 1066-1076, 2013 (**Chapter 2**)
2. Iacovides S, Avidon I, Bentley A, Baker FC. Reduced quality of life when experiencing menstrual pain in women with primary dysmenorrhea. *Acta Obstetricia et Gynecologica Scandinavica* (AOGS), 2013. DOI:10.1111/aogs.12287 (**Chapter 3**)
3. Iacovides S, Baker FC, Avidon I. The 24 hour progression of menstrual pain in women with primary dysmenorrhea when given diclofenac potassium: A randomized, double-blinded, placebo-controlled crossover study. *Archives of Gynecology and Obstetrics*, 2013. DOI: 10.1007/s00404-013-3073-8 (**Chapter 4**)
4. Iacovides S, Avidon I, Bentley A, Baker FC. Diclofenac potassium restores objective and subjective measures of sleep quality in women with primary dysmenorrhea. *SLEEP* 32(8):1019-1026, 2009 (**Chapter 5**)
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Non-accredited publications

1. Iacovides S. Sleep and Pain. *Sleep Matters* 1(1): 4-5, 2010

International conference presentations

The 3rd International World Sleep Congress, Sao Paulo, Brazil, November 2009

Poster presentation: “The effect of diclofenac potassium on sleep in women with primary dysmenorrhoea”

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1. The University of the Witwatersrand’s 5th Cross-Faculty Symposium, Johannesburg, August 2013
Oral presentation: “Women with dysmenorrhoea are hypersensitive to experimental deep muscle pain across the menstrual cycle”
(Awarded first prize for the best presentation in the Faculty of Science)
2. Faculty of Health Science Research Day, Johannesburg 2008
Oral presentation: “The effect of diclofenac potassium on sleep in women with primary dysmenorrhoea”
3. Pain South Africa meeting, Johannesburg, 2008
Oral presentation: “The effect of diclofenac potassium on sleep in women with primary dysmenorrhoea”
4. The 35th Annual Meeting of the Physiological Society of Southern Africa (PSSA), Durban, September 2007
Oral presentation: “The effect of diclofenac potassium on sleep in women with primary dysmenorrhoea”

The thesis is submitted in the optional format, approved by the University of the Witwatersrand’s Faculty of Science, of published and submitted work, with a supporting Introduction and Conclusion. Paper 1 of my peer-reviewed publications (listed above) appears as “part a” of Chapter Two of my thesis. Papers 2, 3 and 4 appear as Chapters Three, Four and Five, respectively.

ABSTRACT

Primary dysmenorrhoea, or painful menstruation in the absence of pelvic pathology, is a common, and often debilitating, gynaecological condition that affects between 45 to 95% of menstruating women. Despite the high prevalence, dysmenorrhoea is often poorly treated, and even disregarded, by health professionals, pain researchers, and the women themselves, who may accept it as a normal part of the menstrual cycle. The overall purpose of this thesis is two-fold: first, to contribute knowledge about the impact and consequences of recurrent severe menstrual pain on pain sensitivity, mood, quality of life and sleep in women with primary dysmenorrhoea, and secondly, to investigate day-time and night-time treatment of recurrent primary dysmenorrhoeic pain. For this thesis, I completed five separate studies on three different groups of young, otherwise healthy women with a history of severe primary dysmenorrhoea, and age-matched controls without dysmenorrhoea.

The first two studies, presented in Chapter 2, addressed the question of whether women with primary dysmenorrhoea are hypersensitive to experimental pain. I used clinically-relevant experimentally-induced muscle pain stimuli (intramuscular injection of hypertonic saline and ischaemia) in referred and non-referred sites of menstrual pain, at different phases of the menstrual cycle. Women with dysmenorrhoea, compared to women without dysmenorrhoea, had increased sensitivity to deep-muscle pain both within the area of referred menstrual pain and at a remote pain-free site. Further, the increased muscle pain sensitivity was evident even in phases of the menstrual cycle when

women did not have menstrual pain, illustrating that the changes in pain perception extend outside of the painful menstruation phase. These findings suggest that women with dysmenorrhoea show long-lasting changes in pain processing possibly because of the recurrent dysmenorrhoeic pain. A secondary aim of the study presented in Chapter 2a, was to determine the impact of menstrual cycle phase on experimentally-induced muscle pain sensitivity in women with and without primary dysmenorrhoea. My results suggest that menstrual cycle phase has no effect on pain sensitivity in either group of women.

As part of my studies, I investigated the impact of dysmenorrhoeic pain on quality of life and mood. I found that women with dysmenorrhoea had a significantly reduced quality of life (Chapter 3) and poorer mood (Chapter 2a and Chapter 5), during menstruation compared to their pain-free follicular phase, and compared to the menstruation phase of the pain-free control women. These data highlight the negative impact that primary dysmenorrhoea has on young women, for up to a few days every month.

Non-steroidal anti-inflammatory drugs (NSAIDs) are often prescribed as the first-line therapy for menstrual pain. Yet, severe dysmenorrhoeic pain is often poorly managed, especially at night, when the pain likely disrupts sleep. I conducted two studies investigating the effectiveness of diclofenac potassium, a readily-available NSAID with a low side-effect profile, compared to placebo, in alleviating severe primary dysmenorrhoeic pain across the day (Chapter 4), and during the night (Chapter 5). I also investigated the effectiveness of diclofenac potassium in improving subjective and

objective sleep quality (Chapter 5). I found that the daily recommended dose (150 mg) of diclofenac potassium, administered at three timepoints across the first 24 hours of menstruation, significantly reduced perceived menstrual pain, compared to placebo. I confirmed that dysmenorrhoeic pain reduces polysomnographic and subjective measures of sleep quality compared with the pain-free follicular phase. I also showed, for the first time, that diclofenac potassium is effective, compared to placebo, in alleviating nocturnal pain, along with restoring subjective sleep quality and polysomnographic measures of objective sleep quality in women with severe primary dysmenorrhoea.

My studies have addressed several gaps in the knowledge about primary dysmenorrhoea. I have shown that women with primary dysmenorrhoea are hypersensitive to deep muscle pain, supporting the hypothesis of other researchers that the recurrent menstrual pain experienced by these women is associated with central sensitisation, and may predispose women with primary dysmenorrhoea to other chronic painful conditions. Therefore, limiting the monthly noxious input into the central nervous systems of these women, by means of effective treatment of dysmenorrhoea, may improve their long-term health. The research presented in this thesis further highlights the efficacy of diclofenac potassium in relieving not only day-time and night-time dysmenorrhoeic pain, but also in restoring objective and subjective pain-induced sleep disturbances in women with dysmenorrhoea. Further, my research has shown that dysmenorrhoeic pain has an immediate negative impact on quality of life and mood during menstruation. The results of this thesis show the multi-factorial impact of dysmenorrhoea and should stimulate further research about the long-term benefits of effective treatment of menstrual pain.

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
ANS	Autonomic nervous system
CNS	Central nervous system
COX	Cyclo-oxygenase
CPP	Chronic pelvic pain
CSS	Central sensitivity syndrome
EEG	Electroencephalography
EMG	Electromyography
EOG	Electro-oculography
FSH	Follicle stimulating hormone
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GI	Gastrointestinal
HPA	Hypothalamic-pituitary-adrenal
IBS	Irritable bowel syndrome
LH	Luteinising hormone
MT	Movement time
NREM	Non-rapid eye movement
NSAIDs	Non-steroidal anti-inflammatory drugs
PGs	Prostaglandins
PET	Positron emission tomography

PGD ₂	Prostaglandin D ₂
PGDS	PGD synthase
PGE ₂	Prostaglandin E ₂
PGF _{2α}	Prostaglandin F _{2α}
PML	Periodic movements of the leg
PMS	Premenstrual syndrome
POMS	Profile of mood states
PPI	Present pain index
PRI	Pain rating index
PSG	Polysomnography
PSQI	Pittsburg Sleep Quality Index
REM	Rapid eye movement
RM-ANOVA	Repeated-measures analysis of variance
ROL	REM sleep onset latency
SE	Sleep efficiency
SOL	Sleep onset latency
Coxibs	Specific COX-2 inhibitors
SWS	Slow wave sleep
TRT	Total recording time
TST	Total sleep time
TWT	Total wake time
VAS	Visual analogue scale
VBM	Voxel-based morphometry

CHAPTER ONE

INTRODUCTION

Primary dysmenorrhoea, or painful menstruation, is a common gynaecological complaint experienced by 45-95% of menstruating women (Proctor and Farquhar 2006). In this introduction, I will discuss the literature on the aetiology and consequences of primary dysmenorrhoea, with a focus on nociceptive pathways, mood, quality of life and sleep. I also will review currently available treatments for dysmenorrhoeic pain, focusing primarily on non-steroidal anti-inflammatory drugs. However, given that many gynaecological symptoms vary in severity across the menstrual cycle, suggesting that gonadal hormones may influence pain sensitivity, a brief description of the normal menstrual cycle and its impact on pain perception, independent of dysmenorrhoea, is first merited.

1.1 The Ovulatory Menstrual Cycle

The ovulatory menstrual cycle is characterised by regulated cyclic variations in hormone production, body temperature and metabolic rate, across a 25-35 day period (see Figure 1 for a summary of plasma hormone concentrations during the menstrual cycle). As described by Vander *et al.* (1998), the follicular (proliferative) phase lasts from the first day of menses, typically referred to as day 1, until ovulation, which occurs around day 14. During menstruation, concentrations of the four predominant reproductive hormones, namely; luteinizing hormone (LH), follicle stimulating hormone (FSH), oestrogen and progesterone, are low. Oestrogen levels progressively increase from around day 5, and rapidly reach a peak towards the end of the follicular phase. The rise in oestrogen stimulates the secretion of LH leading to ovulation around day 14. While oestrogen predominates in the follicular phase, progesterone concentrations remain low. However, in the second half of the menstrual cycle, the luteal (secretory) phase, progesterone is secreted from the corpus luteum, and thus becomes the predominant steroid hormone (Vander *et al.* 1998). There is an increase in body temperature of approximately 0.4°C as well as augmented energy expenditure and sleeping metabolic rates, hypothesised to be driven, at least in part, by increased progesterone levels, in the luteal phase compared with the pre-ovulatory follicular phase (Meijer *et al.* 1992; Driver *et al.* 1996).

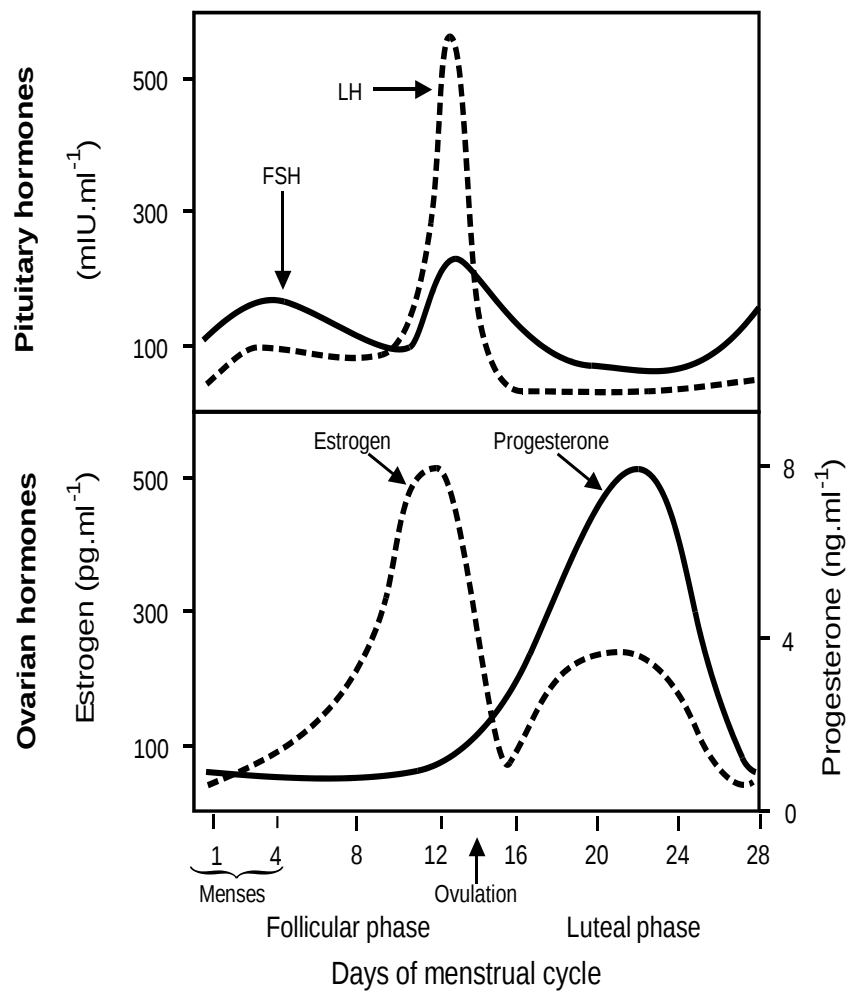


Figure 1. The plasma hormone concentrations during a typical 28-day ovulatory menstrual cycle. Figure adapted from Pocock and Richards (1999) (Pocock and Richards 1999).

The body is widely responsive to the varying endocrine profile across the menstrual cycle. In addition to their reproductive functions, the cyclic variations in gonadal hormone concentrations affect areas of the nervous system that are involved in higher cognitive functions such as mood and pain processing.

1.2 Pain and the Ovulatory Menstrual Cycle

Clinical pain conditions are more common in women than men (Berkley 1997; Pogatzki-Zahn 2013), and, importantly, such pain disorders predominantly appear to affect women of reproductive age (Unruh 1996; Craft 2007). In addition, epidemiological studies demonstrate cyclical exacerbations in several pain conditions, suggesting that gonadal hormones may influence pain perception. While the exact mechanisms underlying these effects remain unclear, it is plausible that female gonadal hormones may alter endogenous pain modulation and analgesia (Fillingim and Ness 2000; Craft *et al.* 2004; Aloisi and Bonifazi 2006).

Indeed, there is evidence suggesting that the hormones oestrogen and progesterone are protective against painful episodes in clinical pain conditions. For instance, women with several clinical pain conditions including fibromyalgia, irritable bowel syndrome (IBS), temporomandibular joint dysfunction, migraine and rheumatoid arthritis report an increased number and severity of painful episodes during the late luteal/premenstrual and menstrual phases of the menstrual cycle, when oestrogen levels either are rapidly falling or very low (Johannes *et al.* 1995; LeResche

2000; LeResche *et al.* 2003; Pamuk and Cakir 2005; Martin 2009; Colangelo *et al.* 2011). For a review on clinical syndromes across the menstrual cycle, refer to Martin, 2009 (Martin 2009).

1.2.1 Pain and the Gonadal Hormones

The transmission of pain involves dynamic and interactive events in the peripheral and central nervous systems. Although the exact neuroanatomy and neurochemistry of nociceptive processing and modulation remain unclear, the current notion of nociceptive processing describes an arrangement which, under normal circumstances, involves a counterbalance between sensitisation and desensitisation (by inhibitory feedback systems) of the system (Fillingim and Ness 2000; Fields *et al.* 2006). Modulation of pain occurs at a variety of sites in the primary afferents, spinal cord, brainstem and cerebrum (Fields and Basbaum 2005). Since gonadal hormone receptors have been identified throughout the nervous system (Deroo and Korach 2006), it is possible that these hormones affect numerous sites simultaneously to modulate the pain experience. Indeed, gonadal hormones have been demonstrated to interact with nociceptive processes at multiple levels of the peripheral and central nervous system (CNS) (Fillingim and Ness 2000; Aloisi and Bonifazi 2006; Puri *et al.* 2006; Roglio *et al.* 2008; Martin 2009). However, the underlying mechanisms and the precise role of gonadal hormones in modulating nociception and pain, are not fully understood, and there is a lack of consistency regarding the relationship between these hormones and pain perception, such that oestrogen and progesterone have paradoxically been observed to generate both antinociceptive and pronociceptive effects on pain pathways (Craft *et al.* 2004; Martin 2009). In the text below, I will briefly summarise the pertinent literature that describes the relationship

between the gonadal hormones and pain perception - focusing mainly on the female gonadal hormones: oestrogen and progesterone.

Gonadal hormones have been found to alter various neuromodulators involved in spinal nociceptive processing, including substance P, the amino acids glutamate and gamma-aminobutyric acid (GABA), as well as various other neurotransmitters, including endogenous opioids, dopamine, noradrenaline and serotonin (Smith 1994; Duval *et al.* 1996; Fields and Basbaum 2005). Oestrogen is believed to be associated with nociception through modulatory effects on GABA receptors, mu (μ) opioid receptors, and nerve growth factor receptors in the dorsal root ganglion (Woolf 1996; Eckersell *et al.* 1998; Aloisi 2003; Smith *et al.* 2006). Similarly, progesterone has been shown to modulate afferent sensory input through the inhibitory GABAergic system. GABA levels in the occipital cortex of humans have been found to decrease across the menstrual cycle, with a negative association between GABA and both oestrogen and progesterone levels (Epperson *et al.* 2002). Since GABA is the main inhibitory neurotransmitter in the CNS, reduced GABA concentrations may result in reduced pain inhibition and hence, increased pain.

High or fluctuating levels of oestrogen also are believed to enhance afferent sensory input through glutamatergic mechanisms (McRoberts *et al.* 2007) or by increased synthesis of neurotrophins (Pezet and McMahon 2006). Furthermore, there is evidence of pronociceptive actions of oestrogen via inflammatory and stress responses (Fillingim and Maixner 1995; Martin 2009). One suggested mechanism by which oestrogen enhances pain is via the release of peripheral cytokines, such as gamma-interferon, which in turn, increases cortisol secretion. Prolonged increases in cortisol

release may promote destruction of muscle, bone and neural tissue, thus establishing the foundation for various chronic pain conditions (Melzack 1999).

On the other hand, oestrogen also displays antinociceptive effects. It has been proposed that oestrogen may reduce sensory neurotransmission via down-regulation or inhibition of transient receptor potential vanilloid subfamily 1 receptors (Xu *et al.* 2008) and glutamate reuptake (Pawlak *et al.* 2005). In addition, oestrogen affects endogenous opioidergic processes at various levels; including the synthesis, absorption, distribution and metabolism of opioids (Craft *et al.* 2004), and has been shown to influence all three primary receptor types (mu, kappa, and delta) mediating the effects of endogenous opioid peptides. Oestrogen activates spinal cord kappa- and delta-opiate receptors (Dawson-Basoa and Gintzler 1998) and affects mu-mediated neurotransmission, with decreased neurotransmission in the CNS during periods of low oestrogen concentration (Smith *et al.* 2006). Negative associations also have been observed between circulating levels of oestradiol and CNS mu-receptor availability during the follicular, compared to the luteal phase (Smith *et al.* 1998). The analgesic effects of oestrogen via the opioid system have also been well documented in animal studies (Maggi *et al.* 1989; Fillingim and Ness 2000; Craft *et al.* 2004). In addition, progesterone and its metabolites, have been reported to exert antinociceptive effects, mainly via the GABA_A receptor complex (Twyman and Macdonald 1992; Frye and Duncan 1994; Belelli and Lambert 2005). Similar to oestrogen, the analgesic effects of progesterone in animals have been documented (Fillingim and Ness 2000; Craft *et al.* 2004).

Investigation of inflammatory models of pain in animals, have shown that oestrogen administration attenuates inflammatory collagen-induced arthritis (Ganesan *et al.* 2008). In addition, an oestrogen receptor-beta agonist was found to inhibit thermal-mediated hyperalgesia after the application of prostaglandin E₂, an inflammatory agent (Leventhal *et al.* 2006). Taken together, these findings propose that oestrogen may exert anti-inflammatory effects that are likely mediated by oestrogen receptor-beta agonism. Furthermore, oestrogen exerts anti-inflammatory effects by reducing the microglia cell's inflammatory response to lipopolysaccharides (Vegeto *et al.* 2001).

Studies involving functional imaging techniques, including positron emission tomography (PET) scans (Smith *et al.* 2006) and functional magnetic resonance imaging (fMRI) (Choi *et al.* 2006; de Leeuw *et al.* 2006), may provide further evidence that the gonadal hormones are involved in the modulation of pain perception. Functional imaging techniques offer objective information on brain activity during the perception of pain, such that interpretations can be made regarding central processing mechanisms (Vincent and Tracey 2010). However, even across these few studies results are not consistent. In two studies, heat pain thresholds in healthy pain-free women were not different during low and high oestrogen conditions (de Leeuw *et al.* 2006; Vincent *et al.* 2011). However, a third study found that during the period of low oestrogen, compared with high oestrogen, healthy pain-free women had enhanced perception to muscle pain induced by hypertonic saline (Smith *et al.* 2006). Inconsistencies may be attributed to the small sample size (de Leeuw *et al.* 2006; Smith *et al.* 2006), and the use of different noxious stimuli. Furthermore, the inconsistent results have been attributed to the fact that oestrogen and progesterone both increased significantly during the luteal compared to the follicular phase in the one study; rendering the interpretation of

the studies results difficult, particularly with regard to each hormones' contribution to pain (Choi *et al.* 2006; Vincent and Tracey 2010).

There also is evidence that the interaction between oestrogen and progesterone may be critical in their impact on pain perception. One study, for example, found that the increased perceived pain intensity associated with high progesterone levels, was significantly reduced with increasing oestradiol levels (Stening *et al.* 2007). Furthermore, there was a tendency towards higher pain thresholds with increasing levels of both oestradiol and progesterone; thus, high serum concentrations of both oestrogen and progesterone were antinociceptive (Stening *et al.* 2007). Such antinociceptive effects also are observed in pregnant women who have increased pain thresholds during the third trimester, a period of high oestrogen and progesterone levels (Watanabe *et al.* 2002).

The results of animal studies also illustrate that the interaction between gonadal hormones and pain perception is complex and not entirely understood (Frye *et al.* 1992; Robbins *et al.* 1992; Gaumond *et al.* 2005; Kuba *et al.* 2006). The hormonal effects on nociceptive processing likely are the result of actions at multiple levels, from peripheral nerves to the highest cortical response, and may exert pronociceptive or antinociceptive effects, depending on the hormone profile. As reviewed by Martin (2009), most studies suggest that the hormonal milieu during the proestrous phase of the the rats oestrous cycle (in which serum oestradiol concentrations peak during early proestrous and decline during late proestrous, and serum progesterone concentrations are low during early proestrous, and peak during late proestrous), may be pronociceptive. It is however, not known whether the high or

fluctuating serum oestradiol concentrations are accountable for the pronociceptive effects during this phase, or whether progesterone might also influence pain perception during the proestrous phase (Martin 2009).

In summary, the net effect of these hormones on pain perception likely is dependant on the sum of their pronociceptive and antinociceptive effects (Martin 2009). Finally, it is important to note that although less is known about the role of other sex hormones, such as testosterone, in the perception of pain, we cannot disregard their possible contributing effects. A very recent study, in fact, suggests that testosterone influences pain processing by affecting descending inhibitory pathways in females (Vincent *et al.* 2013). However, the effects of testosterone appeared to be dependent on oestrogen concentrations, and thus it is likely that hormone constellations are more important than individual hormone levels when considering their effects on pain. Thus, there still is no clear picture of the association between reproductive hormone status and pain.

1.2.2 Experimental Pain across the Ovulatory Menstrual Cycle

The complexity of the relationship between gonadal hormones and pain perception in women is highlighted by the inconsistent, and hence inconclusive, results of investigations on experimentally-induced pain across the menstrual cycle (see Table 1). Human experimental pain models applied to healthy volunteers are useful tools for investigating various aspects of the pain mechanisms, as they create a situation in which healthy volunteers transiently become patients with well-defined

pain in whom sensory manifestations and sensory-motor interactions can be assessed. Moreover, experimental pain models may be valuable in both pharmacological and clinical studies to quantify the sensitivity of the nociceptive system in pain patients, and in predicting clinical pain outcomes (Arendt-Nielsen and Graven-Nielsen 2008). Collectively, research on experimental pain compliments clinical research.

There is a relatively large body of literature on experimental pain perception across the menstrual cycle in normal healthy women. However, studies have been unable to agree on whether a cyclical influence on pain exists, let alone the direction of the effect, should it exist. Some studies suggest that responses to painful stimuli vary across the menstrual cycle, while others argue that experimental pain perception does not vary according to menstrual cycle phase. The details and results of each study on pain perception across the menstrual cycle in healthy women with normal menstrual cycles are presented in Table 1.

Table 1. Summary of human studies, in chronological order, investigating the influence of the normal menstrual cycle on experimental pain responses in healthy, normally cycling women.

Authors, Year	Subjects	Study Results & Outcome Variable Used	Menstrual Phases Studied	Body Location
Herren, 1933	5	Follicular phase: ↑ sensitivity to two-point touch (threshold), ↑ sensitivity to pain discriminations, ↓ tactile sensitivity.	• Premenstrual (5 days menses onset) • Follicular • Late Follicular	Forearm
Robinson & Short, 1977	6	Premenstrual & Menstrual phases: ↑ sensitivity to two-point discrimination thresholds, ↑ sensitivity to pain (Semmes-Weinstein pressure aesthesiometer-20 nylon mono-filaments).	8 menstrual cycles (phases and days not specified)	Breast
Tedford <i>et al.</i> , 1977	12	±1 week after menses with a steady climb until peak at ovulation: ↑ sensitivity to electrical shock aversion thresholds.	• Menstrual (days 1-7) • Postmenstrual (days 8-14) • Ovulatory (days 15-21) • Premenstrual (days 21-28)	Middle & index fingers of “non-preferred” hand (cutaneous)
Goolkasian, 1980	12	Ovulatory Phase: ↑ sensitivity to radiant heat stimulation (dolorimeter). *	• Menstrual (days 1-7) • Postmenstrual (days 8-14) • Ovulatory (days 15-21) • Premenstrual (days 22-28)	Right forearm
Goolkasian, 1983	12	Ovulatory & Menstrual phases: ↑ sensitivity to radiant heat stimulation (dolorimeter) *	• Menstrual (days 1-7) • Postmenstrual (days 8-14) • Ovulatory (days 15-21) • Premenstrual (days 22-28)	Right forearm
Aberger <i>et al.</i> , 1983	18	Premenstrual phase: ↓ sensitivity to ischaemia (threshold & tolerance).	• Premenstrual • Menstrual • Post-menstrual (days not defined)	Non-dominant arm & hand

Authors, Year	Subjects	Study Results & Outcome Variable Used	Menstrual Phases Studied	Body Location
Veith et al., 1984	16	No cycle effects in sensitivity to electric shock pain & cold pressor thresholds. *	• Menstrual (days 2-4) • Follicular (days 8-10) • Ovulatory • Luteal (6-8 days after ovulation) • Premenstrual (11-13 days after ovulation)	Inside of non-dominant wrist (cutaneous electric shock) & dominant hand (cold pressor)
Kuczmierczyk & Adams, 1986	10	No cycle effects on sensitivity to Forgione-Barber pain stimulator (pressure pain threshold & tolerance).	• Menstrual (days 1-4) • Intermenstrual phase (days 7-22) • Premenstrual (days 24-28)	Middle phalanx of index finger of dominant
Kuczmierczyk et al., 1986	10	No cycle effects on sensitivity (Forgione-Barber) pressure pain (tolerance). Intermenstrual phase: ↑ sensitivity to pressure (numeric rating).	• Menstrual (days 1-4) • Intermenstrual phase (days 7-22) • Premenstrual (days 24-28)	Middle phalanx of index finger of dominant
Hapidou & De Catanzaro, 1988	19	Follicular phase: ↓ sensitivity to cold pressor pain (threshold).	• Follicular (days 8-14) • Luteal (days 15-21)	Arm
Amodei & Nelson-Grey, 1989	12	No cycle effects on sensitivity to muscle ischaemia, & pressure (Forgione Barber pressure device) pain (threshold & tolerance).	• Menstrual (days 1-4) • Intermenstrual (days 12-16) • Premenstrual (days 1- 4 before menses onset)	Arm (ischaemia) & middle phalanx of index finger (pressure).
Filligim et al., 1997	11	Midfollicular: ↓ sensitivity to ischemic pain (threshold & tolerance). No cycle effects on thermal sensitivity (threshold & tolerance). †, #	• Midfollicular (days 5-8) • Ovulatory (within 24h of ovulation) • Mid-to-late luteal (days 19-27)	Arm
Pfleeger et al., 1997	11	Luteal phase: ↑ sensitivity to ischaemia (submaximal effort tourniquet test - threshold & tolerance). No cycle effects on verbal descriptors of pain intensity (sensory) & pain unpleasantness (affective). †	• Follicular phase (days 4-9) • Mid-to-late luteal phase (5-10 days after ovulation)	Arm

Authors, Year	Subjects	Study Results & Outcome Variable Used	Menstrual Phases Studied	Body Location
Giamberardino <i>et al.</i>, 1997	10	Luteal phase: ↓ sensitivity to cutaneous, subcutis & muscle electrical stimulation (thresholds) at all sites. Perioovulatory phase: ↑ cutaneous sensitivity, ↑ muscle/subcutis sensitivity.	• Menstrual (days 2-6) • Perioovulatory (days 12-16) • Luteal (days 17-22) • Premenstrual (days 25-28)	Arm, leg & abdomen
Hapidou & Rollman, 1998	36	Follicular phase: ↑ sensitivity pressure pain (tender point count using palpation & digital pressure-dolorimetry).	• Menstrual (days 1-7) • Follicular (days 8-14) • Luteal (days 15-21) • Premenstrual (days 22-28)	Rheumatological tender points
Hellstrom & Lundberg, 2000	22	Luteal phase: ↓ sensitivity (↑ pain thresholds) to cold pressor pain.	• Menstrual (days 2-4) • Luteal (days 20-24)	Dominant hand
Cimino <i>et al.</i>, 2000	18	Menstrual, follicular & luteal phases: ↓ masseter sensitivity (electric algometer pressure pain thresholds). Luteal phase: ↓ temporalis sensitivity (pressure pain threshold).	• Menstrual (day 1) • Follicular (7 ± 2 days after menses) • Perioovulatory (14 ± 2 days after menses) • Luteal (21 ± 2 days after menses)	Masseter & temporalis
Granot <i>et al.</i>, 2001	31	No cycle effects on sensitivity to heat (thermode) pain thresholds. Luteal phase: ↑ latency & ↑ amplitude of pain-evoked potentials by laser stimuli during the follicular phase; ↓ latency & ↓ amplitude of evoked potentials.	• Menses (days 1-2) • Midfollicular (days 5-9) • Ovulatory (days 14-17) • Midluteal (days 21-24)	Thenar eminence of the non-dominant hand (heat) & dorsal superficial radial nerve of hand (laser)
Isselée <i>et al.</i>, 2001	10	Perimenstrual phase: ↑ sensitivity to pressure pain (electronic algometer thresholds) at all sites.	• Mid-to-late Follicular (days 8-12) • Mid-to-late Luteal (days 19-26) • Perimenstrual (days 1, 27, 28)	Masseter, temporalis & thumb muscles

Authors, Year	Subjects	Study Results & Outcome Variable Used	Menstrual Phases Studied	Body Location
Bajaj <i>et al.</i>, 2002	15	Menstrual phase: ↑ sensitivity to pressure, pinch & heat pain (thresholds) at all sites. No cycle effects on sensitivity to tactile threshold (Von Frey hairs) at all sites. †	• Menstrual (days 1-6) • Ovulatory (days 12-16) • Luteal (days 17-22) • Premenstrual (days 25-28)	Arm, thigh, abdomen, lower back
Tassorelli <i>et al.</i>, 2002	14	Luteal phase: ↑ sensitivity to electrical noxious stimuli.	• Follicular (days 8-10) • Luteal (days 6-8 from ovulation)	Biceps femoris
Oshima <i>et al.</i>, 2002	9	No cycle effects on sensitivity to electrical pain thresholds.	• Follicular (day 7) • Luteal (day 21)	Median nerve in index finger of non-dominant hand
Drobek <i>et al.</i>, 2002	10	Perimenstrual: ↓ masseter sensitivity (pressure pain thresholds). No cycle effects on sensitivity to pressure in the temporalis, masseter tactile thresholds (Von Frey filaments), & finger pain stimuli.	• Follicular (days 5-12 after menses) • Luteal (days 16-27) • Perimenstrual (day 28 -day 3 of next menses)	Masseter, temporalis & middle phalanx of 3 rd right-hand finger
Straneva <i>et al.</i>, 2002	27	No cycle effects on sensitivity to ischaemia (submaximal effort tourniquet test thresholds & tolerance times). †, #	• Follicular (4-9 days after menses) • Luteal (8-12 days after LH surge)	Forearm
Sherman <i>et al.</i>, 2005	25	No cycle effects on sensitivity to pressure pain tolerance, palpation pain intensity (VAS), & ischaemia (submaximal effort tourniquet test threshold & tolerance). †, •	• Menses (days 1-3) • Ovulatory (1-2 days after LH-surge) • Midluteal (7-8 days after LH surge) • Late-luteal (12-14 days after LH-surge)	Masseter & temporalis & sites on head, face, neck, back, arms used for evaluation of temporomandibular disorders & fibromyalgia (pressure) & non-dominant arm (ischaemia)

Authors, Year	Subjects	Study Results & Outcome Variable Used	Menstrual Phases Studied	Body Location
Kowalczyk <i>et al.</i> , 2006	21	No cycle effects on sensitivity to cold pressor pain (threshold & tolerance). †, #	• Menstrual (days 2-5) • Follicular (days 6-10) • Ovulatory (within 3 days after LH surge) • Luteal (within 7-12 days after LH surge) • Late luteal (within 13-17 days after LH surge)	Left forearm
Choi <i>et al.</i> , 2006	18	Luteal phase: ↑ sensitivity to thermal pain (VAS) and unpleasantness (VAS). #	• Follicular (days 2-13) • Luteal (16-26)	Non-dominant middle finger
Smith <i>et al.</i> , 2006	8	Follicular phase: ↑ sensitivity to muscle pain (hypertonic saline, VAS). #	• Follicular (days 2-9) (low oestrogen) • 7-9 days later after treatment with oestradiol (high oestrogen)	Masseter
De Leeuw <i>et al.</i> , 2006	9	No cycle effects on heat pain thresholds. #	• Menstrual (days 2-3) • Follicular (days 11-12)	Skin overlying left masseter muscle
Stening <i>et al.</i> , 2007	15	Late luteal phase: ↑ sensitivity to cold pressor pain (thresholds) compared the late follicular phase. #	• Early follicular • Late follicular (preovulation) • Early luteal • Late luteal (exact days not defined)	Left hand
Klatzkin <i>et al.</i> , 2010	49	No cycle effects on sensitivity to cold pressor, heat (thermode) & ischaemic (submaximal effort tourniquet procedure) pain (thresholds, tolerance & intensity & unpleasantness (VAS)). †, #	• Early follicular (days 2-5) • Late follicular (days 7-12) • Luteal (8-12 days after LH surge)	Hand (cold), forearm (heat), arm & hand (ischaemia)

Authors, Year	Subjects	Study Results & Outcome Variable Used	Menstrual Phases Studied	Body Location
Rhudy & Bartley, 2010	41	No cycle effects on sensitivity to suprathreshold electrocutaneous stimulations (nociception flexion reflex) & emotionally charged pictures. Late luteal phase: ↓ pain ratings of suprathreshold stimuli. *, †	• Mid-follicular (days 5-8) • Late-luteal (days 1-6 preceding menses)	Biceps femoris muscle of left leg
Kowalczyk et al., 2010	21	Menstrual & late luteal phases: ↓ sensitivity to mechanical pressure pain (↓ ability to discriminate different intensities). †, #	• Menstrual (days 2-5) • Follicular (days 6-10) • Ovulatory (within 3 days after LH surge) • Luteal (within 7-12 days after LH surge) • Late luteal (within 13-17 days after LH surge)	Fingers (2 nd & 3 rd phalanx of both hands)
Ribeiro-Dasilva et al., 2011	30	Luteal phase: ↓ sensitivity to ischaemic pain (submaximal tourniquet test). No cycle effects on sensitivity to heat & pressure thresholds.	• Follicular (days 4-10 after onset of menses) • Luteal (days 4-9 preceding menses)	Right forearm (ischaemia & heat), Right upper trapezius, right masseter & right ulna (pressure)
Vincent et al., 2011	12	No cycle effects on sensitivity to thermal pain.	• Days 1-2 • Days 10-12 • Days 20-22	Lower abdomen & inner arm
Veldhuijzen et al., 2013	15	Follicular phase: ↑ sensitivity to pressure pain thresholds. †, #	• Menstrual (days 2-4) • Midfollicular (days 6-8) • Periovulatory (day of or after positive ovulatory test) • Midluteal (1 week after ovulation)	Left foot dorsum

* = ovulation confirmed with body temperature, † = ovulation confirmed by LH surge in urine, # = menstrual phase confirmed with hormone assays, ‡ = pelvic ultrasound screening for menstrual phase determination, • = midluteal salivary progesterone, VAS = visual analogue scale.

In summary, studies have shown variable effects of the menstrual cycle on pain sensitivity. Enhanced sensitivity to pain has, for example, been reported after menstruation (Tedford *et al.* 1977; Hapidou and De Catanzaro 1988; Giamberardino *et al.* 1997; Hapidou and Rollman 1998; Ribeiro-Dasilva *et al.* 2011; Veldhuijzen *et al.* 2013), at the time of ovulation (Goolkasian 1980; Goolkasian 1983; Cimino *et al.* 2000; Kowalczyk *et al.* 2010), during the luteal phase (Goolkasian 1980; Hapidou and De Catanzaro 1988; Tassorelli *et al.* 2002; Choi *et al.* 2006), during the premenstrual phase (Fillingim *et al.* 1997; Pfleeger *et al.* 1997; Isselee *et al.* 2001) and during the menstrual phases (Herren 1933; Robinson and Short 1977; Hellstrom and Lundberg 2000; Isselee *et al.* 2001).

In contrast, a number of studies suggest a lack of variability in response to pain across the menstrual cycle (Aberger *et al.* 1983; Veith *et al.* 1984; Kuczmierczyk and Adams 1986; Kuczmierczyk *et al.* 1986; Amodei and Nelson-Gray 1989; Fillingim *et al.* 1997; Hapidou and Rollman 1998; Granot *et al.* 2001; Bajaj *et al.* 2002; Drobek *et al.* 2002; Oshima *et al.* 2002; Straneva *et al.* 2002; de Leeuw *et al.* 2006; Kowalczyk *et al.* 2006; Klatzkin *et al.* 2010; Ribeiro-Dasilva *et al.* 2011; Vincent *et al.* 2011).

The inconsistent findings in the current literature regarding pain sensitivity across the menstrual cycle have been attributed to various experimental methodological concerns including: differences in the choice of experimental pain stimuli, and where these are applied (Sherman and LeResche 2006; Vincent and Tracey 2010), as well as different outcome measures (thresholds versus tolerance) used. Also, in the majority of studies, menstrual cycle phase was arbitrarily divided into functionally distinct phases, based either on the ovarian or endometrial cycle

(Sherman and LeResche 2006; Vincent and Tracey 2010; Pogatzki-Zahn 2013), and importantly, most studies did not measure plasma levels of gonadal hormones (see Table 1). Measurements of plasma gonadal hormone concentrations not only are needed to accurately determine the menstrual cycle phase and confirm ovulation, but also are vital to determine the relationship between hormone levels and pain responses. Importantly, concentrations of the gonadal hormones during each phase vary markedly between women and there is a large inter- and intra-variability in menstrual cycle lengths. Further, approximately one in three or one in four menstrual cycles may be anovulatory in normal women (Metcalf *et al.* 1983). Confirming ovulation is therefore also imperative because if ovulation does not occur, the hormonal milieu in the second half of the menstrual cycle will be distinctly different from that which occurs in a normal ovulatory menstrual cycle. Other factors that have not always been considered in studies to date are whether women have severe premenstrual mood changes, such as with premenstrual dysphoric disorder (Straneva *et al.* 2002), which may impact pain responses.

The diverse range of experimental pain stimuli also contribute to the inconsistent findings across the studies. The choice of experimental pain stimuli used in studies is fundamental for numerous reasons: when assessing pain, it is essential that the pain stimulus is a) reproducible, b) strong enough to elicit a measurable response, c) moderate enough to display individual differences, and d) either meaningful enough to bear some resemblance to a natural physiological or clinical pain, or precise enough to elucidate the basic mechanism of a response to pain (Sherman and LeResche 2006). As shown in Table 1, the pain induction procedures that have been used, include: pressure/mechanical pain (Amodei and Nelson-Gray 1989; Bajaj *et al.* 2002), thermal (Bajaj *et al.* 2002), cold pressor stimulation (Hapidou and De Catanzaro 1988), electrical

stimulation (Giamberardino *et al.* 1997), ischaemia (Aberger *et al.* 1983), pinch (Bajaj *et al.* 2002), tactile stimulation (Bajaj *et al.* 2002), intramuscular injection of hypertonic saline (Smith *et al.* 2006), and pain-evoked potentials by laser stimuli (Granot *et al.* 2001).

It is likely that each painful stimulus results in differential processing of nociceptive afferents (Lynn and Perl 1977). Electrical stimuli, for example, activate all classes of afferent neurons, (i.e. both nociceptive and non-nociceptive fibres), hence producing both painful and non-painful sensations (Gracely 1990; Keefe *et al.* 1991), which may be difficult to distinguish. Electrical stimulation also is confounded by concurrent activated muscle twitches (Arendt-Nielsen and Graven-Nielsen 2008), and this modality has been shown to evoke pain sensations that are less natural than other pain stimuli (Gracely 1990; Fillingim and Ness 2000). On the other hand, thermal stimuli activate A-delta and C-fibers only (Keefe *et al.* 1991). In addition, some stimuli (e.g. ischaemic pain and cold pressor pain) produce a stress response, while others activate endogenous pain regulatory mechanisms (e.g. ischaemic pain) (Pertovaara *et al.* 1982; Maixner *et al.* 1990; Kirschbaum *et al.* 1999). Given that studies have shown enhanced hypothalamic-pituitary-adrenal (HPA) responses to stress during the luteal phase compared with the follicular phase (Kirschbaum *et al.* 1999), a specific hormonal milieu is likely to affect one pain stimulus in a different manner compared to another pain stimulus.

The body site and tissue depth at which these stimuli have been applied also varies and likely contributes to the inconsistencies between studies. Body sites have included the thumb (Haman 1944), index finger (Tedford *et al.* 1977; Kuczmierczyk and Adams 1986; Kuczmierczyk *et al.*

1986; Amodei and Nelson-Gray 1989), forearm (Goolkasian 1983; Straneva *et al.* 2002; Kowalczyk *et al.* 2006), arm (Fillingim *et al.* 1997; Giamberardino *et al.* 1997; Pfleeger *et al.* 1997; Bajaj *et al.* 2002), leg (Giamberardino *et al.* 1997; Bajaj *et al.* 2002), abdomen (Giamberardino *et al.* 1997; Bajaj *et al.* 2002; Vincent *et al.* 2011), lower back (Bajaj *et al.* 2002), foot (Veldhuijzen *et al.* 2013), and masseter and temporalis muscles (Isselee *et al.* 2001; Drobek *et al.* 2002). Several aspects of pain assessment have been shown to vary according to body location; particularly with respect to the proximity to the reproductive organs (Robinson and Short 1977; Klonoff *et al.* 1993; Giamberardino *et al.* 1997). The tissue depth at which pain is applied is also likely to play a role in the inconsistent findings since hyperalgesia has been reported to differ in the skin compared to subcutaneous tissue and compared to deep muscle tissue (Vecchiet *et al.* 1990; Giamberardino *et al.* 1993). Furthermore, there is some evidence supporting that nociceptive activity arising from deep tissues, such as muscle, is under greater inhibitory influence than activity from cutaneous sites (Mense 1990).

Another methodological concern that may be accountable for the inconsistent findings of studies investigating pain sensitivity across the menstrual cycle is that of the measurement of the pain response. Researchers have used various pain response outcomes, including: pain threshold, pain tolerance, and visual analogue scales (VAS) to measure pain intensity. It has been argued, for example, that tolerance measures may constitute a learned component of pain which is a more sensitive index of psychological, motivational and cultural factors affecting the experience of pain, while measures of pain threshold constitute an unlearned component of pain more reflective of pure physiological aspects of pain perception (Weisenberg *et al.* 1975; Wolff 1978). The VAS is widely used as an effective method of assessing clinical and experimental pain, as it

has been shown to produce consistent and reliable measures of pain intensity and pain unpleasantness (Revill *et al.* 1976; Price *et al.* 1983; Price *et al.* 1994; Coll and Ameen 2006).

Collectively, as seen in Table 1, differences in the methodology of the studies render it difficult to compare outcomes and to reach agreeable compatible conclusions about the influence of the menstrual cycle phase on pain perception in women with normal menstrual cycles. Even the two reviews that used forms of meta-analyses of several experimental studies about pain reactivity in healthy women across the menstrual cycle are not in agreement. Riley *et al.*, (1999) concluded that there are reduced pain thresholds during the luteal compared to the follicular phase of the menstrual cycle, for almost every stimulus modality used, including pressure, cold pressor, thermal heat and ischaemic muscle pain (Riley *et al.* 1999). In a more recent review of 19 studies, including studies conducted after 1999, Martin (2009) reclassified the menstrual cycle into early, mid-, and late follicular and luteal phases, since the hormonal milieus at the various stages of both the follicular and luteal phases vary vastly. Of the 19 studies examined, 7 reported increased pain perception during the late luteal or early follicular phases (low or declining serum oestrogen and progesterone concentrations), 5 reported increased pain sensitivity during the late follicular and early luteal phases (rising serum oestrogen and rising serum progesterone concentrations), and 6 studies reported no differences in pain sensitivity across the menstrual cycle (Martin 2009). This meta-analysis therefore concluded that the literature about the impact of menstrual cycle phase on pain sensitivity is still inconclusive (Martin 2009).

In my studies described in Chapter 2, I confronted the methodological concerns described above. I confirmed menstrual cycle phase with biological markers (plasma oestrogen and progesterone

concentrations, and ovulatory kits which detect the LH surge in urine), I used a within-subject design to account for many of the difficulties involved with the interpretation of pain perception, including the influence of interactions between biological variables (such as genetics, body size, muscle mass, pain inhibitory pathways and CNS variation) and psychological variables (anxiety, depression and culture); all of which vary considerably between individuals. I also confirmed the absence of severe premenstrual syndrome in the participants, using the validated Penn Daily Symptom Rating Form (Freeman *et al.* 1996), and ensured normal psychological status, using the validated General Health Questionnaire (Goldberg *et al.* 1976). Further, given that mood alters pain perception (Sherman and LeResche 2006; Tu *et al.* 2010), I assessed mood thoroughly using the profile of mood states (POMS) questionnaire, a validated scale of current mood (McNair *et al.* 1992). Finally, I investigated two groups of women: those with and without severe primary dysmenorrhoea, and used two clinically-relevant and effective experimental pain stimuli (hypertonic saline and ischaemia). Pain severity was assessed using the VAS, a validated and effective scale which produces consistent and reliable measures of pain intensity (Revill *et al.* 1976; Price *et al.* 1983; Price *et al.* 1994; Coll and Ameen 2006).

Intramuscular injection of the algescic substance, hypertonic saline, is a better nociceptive and more clinically relevant method of inducing deep muscle pain than electrical stimulation, and has been found to produce no *in vitro* or *in vivo* toxicity (Kellgren 1938; Graven-Nielsen *et al.* 1997; Stohler and Kowalski 1999; Svendsen *et al.* 2005; Hodges *et al.* 2009). Injection of hypertonic saline has been shown to induce a mild, acute muscular pain that closely reproduces clinical musculoskeletal pain in both subjectively perceived quality, and in its effects on motor performance (Graven-Nielsen *et al.* 1997). Hypertonic saline is believed to excite wide dynamic

range neurons (Ro and Capra 1999), possibly via activation of group III (thinly myelinated A-delta fibres) and group IV (unmyelinated C-fibres) muscle nociceptors to produce both a local area of transient pain and referred pain (Paintal 1960; Iggo 1961; Kumazawa and Mizumura 1977; Graven-Nielsen *et al.* 1997; Graven-Nielsen *et al.* 2002). Currently, hypertonic saline has only been used in one study to induce a deep-muscle pain in normally cycling healthy women under different hormonal conditions (Smith *et al.* 2006).

Another accepted method of inducing deep-muscle pain is by inducing tissue ischaemia (Svensson and Arendt-Nielsen 1995). By occluding blood flow to a group of muscles using a tourniquet, and by voluntarily contracting the muscle-group to increase the use of oxygen by the muscles, the muscles become ischaemic and pain is produced (Maixner *et al.* 1990; Svensson and Arendt-Nielsen 1995). The involved mechanisms of deep-muscle pain after ischaemic contractions are complex and not fully understood. However, it has been suggested that ischaemic contractions result in the accumulation of various substances such as potassium, adenosine and lactate, which excite muscle nociceptors or sensitise nociceptors to respond to muscle contractions that are normally non-painful (Newham and Mills 1999; Grace *et al.* 2001; Mense and Simons 2001). In addition, theories on tourniquet-induced ischaemic pain support the role of C-fibres in the transmission of pain, while A-fibre conduction is believed to be abolished during an ischaemic event (Chabel *et al.* 1990; Loram *et al.* 2007). Ischaemia has been previously used as a method for inducing experimental pain in normally cycling healthy women across the menstrual cycle (see Table 1) (Aberger *et al.* 1983; Amodei and Nelson-Gray 1989; Fillingim *et al.* 1997; Pfleeger *et al.* 1997; Straneva *et al.* 2002; Sherman *et al.* 2005; Klatzkin *et al.* 2010; Ribeiro-Dasilva *et al.* 2011).

In the section above I have discussed the literature pertaining to pain perception across the menstrual cycle in women who have normal ovulatory menstrual cycles and who do not experience menstrual pain. Many healthy women of reproductive age experience recurrent monthly menstrual pain, a common gynaecological complaint known as primary dysmenorrhoea. Interestingly, research suggests that the recurrent menstrual pain experienced by women with primary dysmenorrhoea may make these women more susceptible to painful stimuli, not only during menstruation, but also in the pain-free phases of their menstrual cycles. Therefore, in the next section of this introduction I will discuss the prevalence and aetiology of primary dysmenorrhoea, before discussing studies that have investigated the perception of experimental pain across the menstrual cycle in these women.

1.3 Dysmenorrhoea

1.3.1 Definition of Dysmenorrhoea

Dysmenorrhoea, defined as painful menstrual cramps of uterine origin, is the most common gynaecological condition among women of reproductive age (Coco 1999). Despite its common occurrence, however, it is under-diagnosed and under-treated (Campbell and McGrath 1997; Coco 1999; Proctor and Farquhar 2006). Based on pathophysiology, dysmenorrhoea can be subclassified as either primary or secondary dysmenorrhoea (Proctor and Farquhar, 2006).

Primary dysmenorrhoea is defined as painful, spasmodic cramping in the lower abdomen, just before and/or during menstruation, in the absence of any discernable macroscopic pelvic

pathology (Dawood 1987). The onset of primary dysmenorrhoea usually occurs in adolescence, at or shortly after (6-24 months) menarche (Hofmeyr 1996; Dawood 2006). The onset of primary dysmenorrhoeic pain usually has a clear and predictable temporal pattern, beginning just before or at the start of menstruation (Dawood 1987; Harel 2008). The pain typically lasts for 8-72 hours, is most severe during the first or second day of menstruation, and may radiate to the back and thighs (Hofmeyr 1996; Proctor *et al.* 2002; Ruoff and Lema 2003). In addition, systemic symptoms such as nausea, vomiting, diarrhoea, fatigue and insomnia frequently accompany the pain (Hofmeyr 1996; Ruoff and Lema 2003).

Secondary dysmenorrhoeic pain, in contrast, may originate from a number of identifiable pathological conditions, including endometriosis, adenomyosis, fibroids (myomas) and pelvic inflammatory disease. The onset of secondary dysmenorrhoea can occur any time, usually more than 2 years, after menarche, and depending on the underlying condition, may be accompanied by other gynaecological symptoms such as intermenstrual bleeding and menorrhagia. In addition, the timing and intensity of secondary dysmenorrhoeic pain during the menstrual cycle may be constant or diffuse, and is not necessarily associated with menses (Hofmeyr 1996; Proctor and Farquhar 2006). While women with secondary dysmenorrhoea share some of the same characteristics to those of women with primary dysmenorrhoea, the focus of this thesis is on primary dysmenorrhoea.

1.3.2 Prevalence of Primary Dysmenorrhoea

The prevalence of primary dysmenorrhoea is highly underestimated, yet difficult to determine, because few affected women seek medical treatment, despite the substantial distress experienced, as many consider the pain to be a normal part of the menstrual cycle rather than a disorder (Wong 2010); thus, many cases remain undocumented (Gould 1998; Jones 2004; Chen *et al.* 2006; Daley 2008). Due to the different definitions of the condition, and the lack of standard methods for assessing severity of dysmenorrhoea, prevalence estimates vary between 45 and 95% of menstruating women (Jamieson and Steege 1996; Proctor and Farquhar 2006; Unsal *et al.* 2010), with very severe primary dysmenorrhoea estimated to affect approximately 10-25% of women of reproductive age (Andersch and Milsom 1982; Dawood 1987; Sundell *et al.* 1990; Hofmeyr 1996). As such, dysmenorrhoea appears to be the most common gynaecological disorder in women irrespective of nationality and age (Harlow and Park 1996; Proctor and Farquhar 2002; Patel *et al.* 2006).

1.3.3 The Aetiology of Primary Dysmenorrhoea

The most widely accepted explanation for the pathogenesis of primary dysmenorrhoea is the overproduction of uterine prostaglandins (PGs) (Dawood 1987). PGs are ubiquitously distributed intracellular substances which are derived from long-chain polyunsaturated fatty acids such as arachidonic acid, a common component of cell membrane phospholipids (Hayaishi and Matsumura 1995). PGs have been shown to have a range of biological effects on

a wide variety of physiological as well as pathological activities including pain, inflammation, body temperature, and sleep regulation (Hayaishi and Matsumura 1995).

Prostaglandin synthesis is limited by the availability of the free fatty acid precursors for arachidonic acid, which is regulated by cyclic adenosine phosphate. Via cyclic adenosine phosphate, PG production can be stimulated by substances such as adrenaline, peptide hormones and steroid hormones, but also by mechanical stimuli and tissue trauma (Vander *et al.* 1998; Funk 2001). Arachidonic acid is derived from phospholipids by the lysosomal enzyme phospholipase A₂. The stability of lysosomal activity is regulated by several factors, one of which is progesterone levels; high progesterone levels tend to stabilise the activity of lysosomes, while falling levels tend to labilise lysosome activity (Dawood 1995; Hofmeyr 1996). Therefore, the decrease in progesterone that accompanies the regression of the corpus luteum in the late luteal phase of the menstrual cycle results in the removal of this stabilising effect on endometrial lysosomes, the release of phospholipase A₂, menstrual flow and hydrolysis of phospholipids from the cell membrane to generate additional arachidonic acid (see Figure 2). Consequently, the enduring availability of arachidonic acid together with the intracellular destruction and tissue trauma during menstruation, favour the production of PGs (Dawood 1995).

All women have increased levels of PGs during the luteal phase compared with the follicular phase of ovulatory cycles. However, there is evidence that, compared with eumenorrhoeic women, dysmenorrhoeic women have higher levels of PGs, as measured in luteal phase endometrial biopsies, endometrial jet washings and menstrual fluids (Chan and Hill 1978;

Dawood 2006). Higher circulating levels of PGs (PGF_{2α} and PGE₂) have been reported in women with dysmenorrhoea compared with asymptomatic women during menstruation, and these PG levels are highest during the first 48 hours of menses, when symptoms peak (Lundstrom and Green 1978; Dawood 1987; Hofmeyr 1996; Coco 1999). Furthermore, the severity of menstrual pain and associated symptoms of dysmenorrhoea are directly proportional to the amount of PGs released (Chan *et al.* 1981; Dawood 2006). In addition, clinical administration of exogenous PGs results in uterine contraction and often also produces the same systemic symptoms that frequently accompany dysmenorrhoea, including nausea, vomiting and diarrhoea (Dawood 1995; Coco 1999). Taken together, these findings, together with many clinical trials which demonstrate the effective relieve of dysmenorrhoeic pain through PG suppression (see Section 1.3.7), support the hypothesis that PGs are responsible for the painful uterine contractions and the associated systemic symptoms that accompany dysmenorrhoeic pain.

On the basis that exposure of the endometrium to luteal phase progesterone is crucial for the increased production of uterine PGs, dysmenorrhoea is believed to occur only in ovulatory menstrual cycles (Dawood 1987); this notion has, however, more recently been challenged in a study in which basal body temperature was used to distinguish between ovulatory and spontaneous anovulatory menstrual cycles. There was no difference in the severity of menstrual symptoms, including pain, between ovulatory and anovulatory menstrual cycles in women with dysmenorrhoea (Espin Lopez *et al.* 2010). Nevertheless, it currently is believed that primary dysmenorrhoea does result from the enhanced release of PGs, allegedly from

disintegrating cells during endometrial sloughing, which causes myometrial hypercontractility, resulting in ischaemia and hypoxia of the uterine muscle, and, ultimately, pain (Dawood 1987).

There are nine classes of PGs: PGA through PGI; within which individual prostaglandins are denoted by numerical subscripts. The two types of PGs that are implicated in the pathogenesis of primary dysmenorrhoeic pain are $\text{PGF}_{2\alpha}$ and PGE_2 ; however, $\text{PGF}_{2\alpha}$ appears to be of particular importance (Ruoff and Lema 2003). While PGE_2 may result in either myometrial contraction or relaxation, $\text{PGF}_{2\alpha}$ always causes potent vasoconstriction of uterine blood vessels, and myometrial contractions (Hofmeyr 1996; Ruoff and Lema 2003; Harel 2004). There also is evidence that $\text{PGF}_{2\alpha}$ lowers the threshold for pain perception by sensitising nerve endings to pain (Hofmeyr 1996; Ruoff and Lema 2003; Harel 2004).

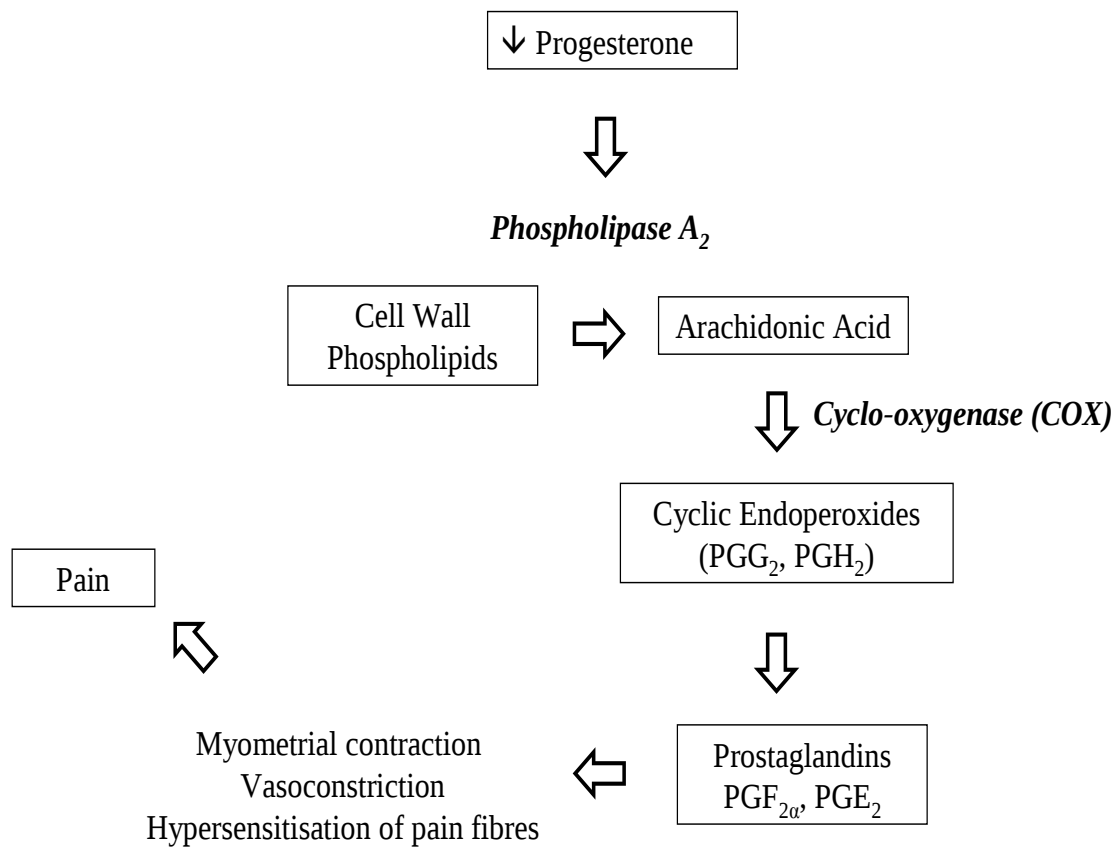


Figure 2. The arachidonic acid cascade displaying the cyclooxygenase (COX) pathway, the biosynthesis of cyclic endoperoxides (PGG₂ and PGH₂) and finally the synthesis of prostaglandins (PGF_{2α} and PGE₂). Prostaglandins F_{2α} and E₂ mediate myometrial contractions, vasoconstriction, hypersensitisation of pain nerve fibres and, ultimately, pain. Enzymes are shown in bold italics. Figure modified from Harel (2004).

Coupled with their elevated PG levels, dysmenorrhoeic women have higher levels of uterine activity during menstruation compared with asymptomatic women; basal or resting uterine tone (> 10 mm Hg), active intrauterine pressure (> 120 mm Hg), frequency of uterine contractions, and uncoordinated uterine contractions all are greater in dysmenorrhoeic women (Akerlund 1979; Dawood 1995; Hofmeyr 1996; Dawood 2006). Furthermore, studies investigating uterine blood flow using Doppler ultrasonography, have shown that the strong and abnormal uterine contractions in women with dysmenorrhoea during menstruation, are associated with reduced uterine blood flow and resultant myometrial ischaemia, and hence pain (Altunyurt *et al.* 2005). Thus, during menstruation, excessive release of PGs by the endometrium results in hypercontractility of the uterus, and subsequent uterine muscle ischaemia and hypoxia (Dawood 1995; Hofmeyr 1996). The contraction of the ischaemic uterus therefore is the likely cause of dysmenorrhoeic pain.

In addition to PGs, vasopressin has been implicated in the aetiology of primary dysmenorrhoea, although the involvement of vasopressin remains controversial (Dawood 2006). Limited studies have shown elevated circulating serum arginine vasopressin levels in women with primary dysmenorrhoea during menstruation (Ekstrom *et al.* 1992; Akerlund 2004). Higher arginine vasopressin levels result in dysrhythmical uterine contractions, which would ultimately contribute to the pain by causing further uterine hypoxia and ischaemia (Akerlund 1979). In contrast, other studies have not found increased plasma vasopressin levels in women with primary dysmenorrhoea (Baker *et al.* 1999a; Valentin *et al.* 2000). Also, a vasopressin antagonist had no effect on menstrual pain, intrauterine pressure and uterine blood flow (Valentin *et al.* 2000).

There also is some evidence that dysmenorrhoea is not merely a disorder noticeable during the menstruation phase of the menstrual cycle. A recent study investigating cytokine gene expression profiles, showed that, throughout the menstrual cycle, women with primary dysmenorrhoea, compared to controls, exhibited a shift in the balance between expression patterns of pro-inflammatory cytokines and TGF-beta family member genes related to anti-inflammatory responses, with up-regulation of genes coding for pro-inflammatory cytokines and down-regulation of genes related to anti-inflammatory responses (Ma *et al.* 2013). In addition, some studies have found that dysmenorrhoeic women present with elevated levels of prolactin in the luteal phase (Litschgi and Glatthaar 1978; Ylikorkala *et al.* 1979; Baker *et al.* 1999a) compared with other phases of the menstrual cycle. Also, women with primary dysmenorrhoea have been found to have higher nocturnal body temperatures, altered sleep, and increased morning oestrogen concentrations compared to asymptomatic women, in three different phases of the menstrual cycle, namely, the mid-follicular, mid-luteal, and menstruation phases (Baker *et al.* 1999a). Therefore, even in the absence of pain, women with dysmenorrhoea may have distorted hormonal and cytokine profiles compared with women without menstrual-associated disorders. It remains unclear, however, whether the altered cytokine and hormonal profiles of women with recurrent menstrual pain translates to other physiological abnormalities outside of the menstruation phase, such as altered processing and perception of pain.

1.3.4 Pain Sensitivity in Women with Dysmenorrhoea

The first study alluding to a possible increase in pain sensitivity across the menstrual cycle in women with dysmenorrhoea compared to women without dysmenorrhoea, was conducted in 1944 (Haman 1944). In this study, dysmenorrhoeic women had lower pain thresholds to a pressure stimulus applied to the thumb, compared to non-dysmenorrhoeic women, in all menstrual cycle phases (Haman 1944). Since this first account of an increased sensitivity to pressure pain in dysmenorrhoeic women compared to women without dysmenorrhoea, several studies have investigated whether pain perception differs between dysmenorrhoeic and non-dysmenorrhoeic women at different phases of the menstrual cycle. However, the results are inconclusive.

Several studies report that no differences exist in the perception of experimental pain, including ischaemic pain, heat pain, and electrical stimulation of the skin, between dysmenorrhoeic and non-dysmenorrhoeic women (Aberger *et al.* 1983; Amodei and Nelson-Gray 1989; Brinkert *et al.* 2007). On the other hand, other studies report that women with dysmenorrhoea have an enhanced perception of laser pain-evoked potentials (Granot *et al.* 2001), heat pain (Goolkasian 1983; Bajaj *et al.* 2002; Vincent *et al.* 2011), pressure pain (Bajaj *et al.* 2002) and electrical pain stimuli (Giamberardino *et al.* 1997) applied to the abdomen, lower back and extremities, compared to non-dysmenorrhoeic women (Giamberardino *et al.* 1997; Bajaj *et al.* 2002; Vincent *et al.* 2011).

As is the case for studies investigating pain sensitivity in women with normal, pain-free menstrual cycles (see Section 1.2.2), it is important to consider menstrual cycle phase when

investigating pain sensitivity in women with primary dysmenorrhoea since gonadal hormones may impact pain perception (as discussed in Section 1.2.1). Also, menstrual cycle phase is of particular importance when investigating pain sensitivity in women with dysmenorrhoea, because it is possible that the perception of pain is altered in the presence of background dysmenorrhoeic pain (during menstruation) compared to pain-free phases of the menstrual cycle.

1.3.4.1 Experimental Pain across the Ovulatory Menstrual Cycle in Women with Dysmenorrhoea

Studies investigating pain sensitivity across the menstrual cycle in women with dysmenorrhoea are inconsistent and inconclusive. Women with dysmenorrhoea have been reported to have reduced cold pain thresholds during the luteal phase compared with the follicular phase (Hapidou and De Catanzaro 1988), reduced heat and pressure pain thresholds during the menstrual phase compared with all other phases of the menstrual cycle (Bajaj *et al.* 2002), and heightened electrical pain thresholds during the late luteal phase (Giamberardino *et al.* 1997). Other studies, however, report that thermal (Granot *et al.* 2001; Vincent *et al.* 2011), ischaemic, and pressure pain perception (Amodei and Nelson-Gray 1989) do not vary according to menstrual cycle phase in women with dysmenorrhoea.

The methodological concerns, including stimulus site, pain modality, and range of outcome measures used, which influence pain sensitivity in women with pain-free menstrual cycles (Section 1.2.2) also apply here. Studies on pain perception across the menstrual cycle in women with dysmenorrhoea have used a diverse range of stimulations to induce experimental pain,

including: pressure (Amodei and Nelson-Gray 1989; Bajaj *et al.* 2002), heat (Granot *et al.* 2001; Bajaj *et al.* 2002; Vincent *et al.* 2011), cold pressor stimulation (Hapidou and De Catanzaro 1988), electrical stimulation (Giamberardino *et al.* 1997), ischaemia (Aberger *et al.* 1983; Amodei and Nelson-Gray 1989), pinch (Bajaj *et al.* 2002), tactile stimulation (Bajaj *et al.* 2002), and pain-evoked potentials by laser stimuli (Granot *et al.* 2001).

As is the case with studies on women without dysmenorrhoea, a variety of sites have been used to induce experimental pain in women with dysmenorrhoea, including: the thumb (Haman 1944), index finger (Amodei and Nelson-Gray 1989), forearm (Goolkasian 1983), upper arm (Giamberardino *et al.* 1997; Bajaj *et al.* 2002), leg (Giamberardino *et al.* 1997; Bajaj *et al.* 2002), abdomen (Giamberardino *et al.* 1997; Bajaj *et al.* 2002) and lower back (Bajaj *et al.* 2002). Menstrual pain is referred to the abdomen in 70 - 90% of women (Montero *et al.* 1999), and to the lower back in 40% of women (Tissot and Messing 1995). However, to date, only three studies have compared pain sensitivity both within and outside areas of referred menstrual pain (Giamberardino *et al.* 1997; Bajaj *et al.* 2002; Vincent *et al.* 2011). Giamberardino *et al.* (1997) found that women with dysmenorrhoea had lower pain thresholds to electrical stimulation during the perimenstrual phase (but not during the luteal phase) for muscle and subcutaneous stimulations at both the abdomen (within the area of referred menstrual pain) and limb sites (outside the area of referred menstrual pain). Similarly, Bajaj (2002) reported hyperalgesia to heat and pressure stimulations both within (abdomen and lower back) and outside (arm and leg) areas of referred menstrual pain during the menstrual phase in dysmenorrhoeic women. The authors hypothesise that these findings are indicative of a spinal mechanism of central hyper-excitability induced by recurrent moderate-to-severe menstrual pain (Bajaj *et al.* 2002). More

recently, a study by Vincent *et al.* (2011) substantiated other reports that women with dysmenorrhoea are more sensitive than controls to thermal pain both within (abdomen) and outside (arm) areas of referred menstrual pain. In contrast to the other two studies, the increased pain sensitivity was evident throughout the menstrual cycle: during the menstruation (days 1-2) phase, the follicular phase (days 10-12), and the luteal phase (days 20-22) (Vincent *et al.* 2011).

In terms of tissue depth, dysmenorrhoeic women have shown hyperalgesia to electrical stimulation in the areas of referred menstrual pain for deep tissues such as muscle and subcutaneous tissue (Giamberardino *et al.* 1997), however, the hyperalgesia does not extend to the skin (Giamberardino *et al.* 1997; Brinkert *et al.* 2007). This finding is in agreement with other studies that report that structures that become hyperalgesic under recurrent visceral pain conditions are primarily muscles, with lesser influence on subcutaneous tissues and even less on the skin (Vecchiet *et al.* 1990; Giamberardino *et al.* 1993).

Based on the diverse study designs and findings presented above, it still remains unclear whether or not women with primary dysmenorrhoea are hypersensitive to pain during the painful menstruation phase and/or during other pain-free phases of the menstrual cycle. In my studies described in Chapter 2, I address many methodological concerns to further investigate whether muscle pain responses differ between women with and without primary dysmenorrhoea at different phases of the menstrual cycle.

1.3.5 Classification of Primary Dysmenorrhoea as a Central Sensitisation Syndrome

While studies of experimental pain have not yet confirmed that women with dysmenorrhoea are hypersensitive to pain, it has been suggested that the repeated monthly painful episodes may result in the development of central sensitivity to pain (Yunus 2007; Yunus 2008). Central sensitisation is defined as an abnormal augmentation of pain by mechanisms within the CNS, and therefore represents a state where the response to normal peripheral inputs is greatly enhanced (Woolf 2004; Woolf 2007). This heightened excitability of nociceptive projection neurons not only increases their sensitivity to inputs from afferents from damaged or inflamed sites, but also to other convergent inputs (Sessle 2007). Primary dysmenorrhoea has been classified as a member of the central sensitivity syndromes (CSS) together with several other clinical conditions including fibromyalgia and tension-type headaches (Yunus 2007; Yunus 2008). These syndromes are characterised by pain hypersensitivity in the absence of tissue injury, inflammation, or a lesion to the nervous system (Woolf 2007; Yunus 2007).

Indeed, compared to non-dysmenorrhoeic women, research indicates that otherwise healthy women with dysmenorrhoea may have a variation in the mode of systemic pain processing; where the peripheral nociceptive message generated by the reproductive organs during menstruation is amplified, thus causing an increased excitability of somatovisceral convergent neurons in the spinal cord, and ultimately, increased pain perception (Granot *et al.* 2001; Bajaj *et al.* 2002). Possible consequences of prolonged massive afferent visceral barrage and hence, increased neuronal input into the CNS, are functional and structural alterations throughout the CNS, including central sensitisation to pain (Giamberardino 1999; Granot *et al.* 2001; Bajaj *et al.*

2002). Below, I will briefly discuss the evidence suggesting that recurrent pain is associated with central sensitisation to pain.

Recent studies have demonstrated significant differences between the brains of otherwise healthy women who experience moderate-to-severe dysmenorrhoeic pain and those of non-dysmenorrhoeic women; including differences in central activity induced by noxious skin stimulation (Vincent *et al.* 2011), cerebral metabolism (Tu *et al.* 2009), and cerebral structure (Tu *et al.* 2010).

Functional magnetic resonance imaging recently demonstrated that activity in the entorhinal cortex, a region that has been implicated in enhanced pain perception mediated by anxiety and anticipation (Ploghaus *et al.* 2001; Fairhurst *et al.* 2007), may explain the increased response to thermal pain that was found in women with dysmenorrhoea, even in the absence of menstrual pain (i.e. during non-menstrual phases) (Vincent *et al.* 2011). Furthermore, during menstruation, control women displayed deactivation of brain regions in response to experimental noxious thermal stimulation; a phenomenon that was not observed in the women with dysmenorrhoea (Vincent *et al.* 2011).

In 2009, Tu *et al.* used fluoro-deoxyglucose PET in 17 women with primary dysmenorrhoea and 16 pain-free controls to demonstrate that primary dysmenorrhoea is associated with abnormal metabolic changes in several areas in the brain involved in pain processing (Tu *et al.* 2009). When experiencing menstrual pain, compared to a pain-free phase of the menstrual cycle, women with dysmenorrhoea showed increased regional glucose metabolism in thalamic,

orbitofrontal and prefrontal areas, and decreased regional metabolism in lateral somatic sensorimotor areas (Tu *et al.* 2009). These presentations of hyper- and hypo-metabolic cerebral regions were found to be unique to menstrual pain; they were not evident in the controls, and they differ from those observed in acute visceral pain conditions and other kinds of persistent pain (Derbyshire 2003; Apkarian *et al.* 2005; Kupers and Kehlet 2006; Kulkarni *et al.* 2007). The authors suggest that disinhibition of thalamo-orbitofrontal-prefrontal networks may contribute to the generation of pain and increased pain sensitivity in women with primary dysmenorrhoea, possibly by maintaining spinal and thalamic sensitisation (associated with chronic visceral pain) and by increasing negative emotion/affect (Tu *et al.* 2009).

Given the results of altered brain metabolism in women with dysmenorrhoea, and that repeated painful episodes experienced by women with dysmenorrhoea may induce structural and functional changes within the CNS, the same group of researchers further investigated the brain morphology in women with and without dysmenorrhoea using an optimised voxel-based morphometry (VBM) approach (Tu *et al.* 2010). Compared to healthy controls, abnormal volume changes in the gray matter of women with primary dysmenorrhoea were observed; in particular, abnormal decreases were observed in regions of the brain involved in pain transmission and higher level sensory processing, while increases were observed in regions involved in pain modulation and endocrine function regulation (Tu *et al.* 2010). Although the functional consequences of this central reorganisation remain to be established, the authors suggest that these changes support a combination of impaired pain inhibition and amplified pain facilitation (Tu *et al.* 2010). Importantly, the changes in gray matter volume were evident even when the women were in a pain-free phase of the menstrual cycle, highlighting that lasting central changes

may occur in recurring pain conditions, and not just chronic pain conditions. This hypothesis is further supported by the observation of similar morphological brain changes (using VBM), specifically decreases in gray matter volume, in other recurrent or chronic pain states, including irritable bowel syndrome (IBS) (Davis *et al.* 2008; Blankstein *et al.* 2010) and chronic pelvic pain (CPP) (As-Sanie *et al.* 2012). Although the changes in gray matter volume may vary between pain states, and may depend on the brain structures involved, as well as pain duration and pain incidence (persistent or intermittent), these changes support the theory that prolonged nociceptive input into the CNS can generate functional and structural modifications throughout the nervous system, and can alter the processing of pain within the CNS (Marcus 1995; Apkarian *et al.* 2005; Hermann *et al.* 2008).

Although primary dysmenorrhoea is not currently classified as a CPP (Howard 2004), it is a frequent co-morbid symptom in women with CPP (Zondervan *et al.* 2001). For example, a recent robust 10-year follow-up study concluded that women with IBS are more likely to experience dysmenorrhoea compared to women without IBS (Olafsdottir *et al.* 2012). This finding is not surprising given that in the clinical setting, a painful condition of one organ can affect the reactivity to painful stimuli of other visceral areas, with at least partially overlapping sensory projection (Giamberardino 2000; Giamberardino *et al.* 2001). Furthermore, other studies report that women who experience both dysmenorrhoea and IBS, or dysmenorrhoea and urinary calculosis, have more menstrual pain, IBS pain and abdominal muscle hyperalgesia (Giamberardino *et al.* 2010), or more menstrual pain, urinary pain and lumbar and abdominal muscle hyperalgesia (Giamberardino *et al.* 2010) compared to women with only one of these painful conditions. The mechanisms underlying this phenomenon, termed “viscero-visceral

hyperalgesia” or “cross-organ sensitisation” are not entirely understood, however, a plausible explanation is that increased nociceptive input to the CNS from one visceral domain (e.g. the reproductive organs), sensitises or increases the excitability of viscerovisceral convergent neurons in the spinal cord. As a result, the central effect of the input from the second visceral location (e.g. the urinary tract) is amplified (Giamberardino 2000) (see review by (Brumovsky and Gebhart 2010)). Regardless of the exact mechanisms involved in producing this visceral interaction, remarkably, effective treatment of one painful condition in one organ decreases pain and symptoms from the other organ. For example, effective treatment of dysmenorrhoea has been shown to significantly decrease pain reactivity from the urinary tract (Giamberardino 2000), as well as IBS and urinary calculosis symptoms (Giamberardino *et al.* 2010) .

Taken together, the recently described evidence of structural and functional modifications within the CNS suggest that women with primary dysmenorrhoea have central changes that persist beyond the time of menstruation, possibly due to the recurrent nociceptive input into the CNS (Marcus 1995; Apkarian *et al.* 2005; Hermann *et al.* 2008). Recently researchers have even suggested that dysmenorrhoea may predispose women to a chronic pain state (As-Sanie *et al.* 2012). Why some women with dysmenorrhoea undergo a transition to a chronic pain state, while others do not, remains unclear. However, it has been hypothesised that central pain modulation (amplification or inhibition) may account for this phenomenon. It is also interesting to speculate whether such central changes contribute to the gender difference in chronic pain conditions (Berkley 1997; Pogatzki-Zahn 2013).

While one potential longterm outcome of primary dysmenorrhoea may be heightened risk for developing other painful conditions later on in life, it also has immediate impact on the daily lives of women due to the effect of pain on daily functioning, quality of life and mood.

1.3.6 Consequences of Primary Dysmenorrhoea

1.3.6.1 Daytime Functioning, Quality of Life and Mood

The painful menstrual cramps experienced by women with dysmenorrhoea can be considerably disabling, having been likened to renal colic pain (Ayan *et al.* 2012). The intense cyclic pain is associated with a restriction of physical activity (Dawood 1995; Chen *et al.* 2006; Patel *et al.* 2006; Chantler *et al.* 2009a), and dysmenorrhoeic pain has been reported to be the primary cause of recurrent short-term school or work absenteeism among young women of child-bearing age. Several longitudinal studies on young dysmenorrhoeic women have revealed that rates of absenteeism in these women range from 34-50% (Andersch and Milsom 1982; Sundell *et al.* 1990). Therefore, dysmenorrhoea not only disrupts the personal lives of these women (Eryilmaz *et al.* 2010), but, given its significant impact on productivity, dysmenorrhoea can ultimately have economic consequences (Hofmeyr 1996; Jones 2004).

Chronic pain is a major contributor to a reduced quality of life (QoL) (Skevington 1998; Laursen *et al.* 2005; O'Connor 2009; Matusiak *et al.* 2010; Souza *et al.* 2011; Langley 2012). Primary dysmenorrhoea presents features of both chronic and acute pain syndromes; it is a recurring pain with a regular onset, however it is of short duration (Baker *et al.* 1999a). However, surprisingly

very little is known about the effect of primary dysmenorrhoeic pain on QoL. Although review articles on primary dysmenorrhoea report that dysmenorrhoeic pain is associated with a reduced QoL (Coco 1999; Proctor and Farquhar 2006), evidence of these claims is limited. Only recently have cross-sectional studies specifically investigated QoL, as a construct, in women who experience dysmenorrhoeic pain. Women with dysmenorrhoea have been shown to exhibit a reduced physical, but not mental component, of QoL (Vincent *et al.* 2011). Women with dysmenorrhoea also have been shown to score significantly lower in the domains of physical and social functioning, physical role functioning, bodily pain and general health perceptions, compared to women who did not report dysmenorrhoea (Barnard *et al.* 2003; Unsal *et al.* 2010). Although these studies report a decrease in health-related QoL in women with dysmenorrhoea, they do not distinguish between primary and secondary dysmenorrhoea (Barnard *et al.* 2003; Unsal *et al.* 2010; Souza *et al.* 2011; Vincent *et al.* 2011), and only one considered the intensity of dysmenorrhoeic pain (Unsal *et al.* 2010). Given that pain severity is a strong predictor of depression and poorer QoL (Bair *et al.* 2003), it is important that studies reporting on QoL consider the intensity of the pain experienced.

Moreover, these studies do not take menstrual cycle phase into account (Barnard *et al.* 2003; Unsal *et al.* 2010; Souza *et al.* 2011; Vincent *et al.* 2011). It therefore remains unknown whether QoL in women with dysmenorrhoea is specifically linked to menstrual pain or is persistently lower, possibly reflecting a different psychological profile, compared to women without dysmenorrhoea. Women with severe premenstrual syndrome, another condition linked to a specific menstrual phase, report a poorer QoL not only in the premenstrual phase but also in the low-symptom follicular phase, compared to controls (Baker *et al.* 2012), and the same may be

true in women with dysmenorrhoea. To address the limitations of previous studies, in the study described in Chapter 3, I investigate, using the validated Short Form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Endicott *et al.* 1993), whether severe recurrent primary dysmenorrhoeic pain affects QoL during menstruation, when the women are experiencing pain, as well as during a non-painful menstrual phase.

Given that pain not only is a sensory experience, but also an emotional event (Taxonomy 1979; Bromm 1995), the effects of dysmenorrhoeic pain on psychological distress and affective states, such as mood, also need to be considered. Epidemiological studies have demonstrated that pain exacerbates psychological distress (Von Korff and Simon 1996; Bair *et al.* 2003). Importantly, the association between pain and anxiety/depression is bidirectional; such that psychological distress can also exacerbate pain (Von Korff and Simon 1996; Bair *et al.* 2003). Numerous studies on pain-free male and female participants have also shown that affective processes can modulate pain; arousing positive emotions and mood are able to reduce pain perception, while arousing negative emotions and mood induces pain facilitation (Weisenberg *et al.* 1984; Zelman *et al.* 1991; Zillmann *et al.* 1996; Weisenberg *et al.* 1998; Rhudy and Meagher 2000; Meagher *et al.* 2001; Wunsch *et al.* 2003; Rainville *et al.* 2005; Rhudy *et al.* 2005; Rhudy and Bartley 2010).

There are surprisingly few reports on emotional distress in women who experience cyclical primary dysmenorrhoeic pain. Evening assessment of mood in one study showed that women with primary dysmenorrhoea were significantly more agitated during menstruation compared to their follicular phase (Baker *et al.* 1999a). Similarly, depression and anxiety have been found to

be strongly associated with menstrual pain, although no distinction was made between women with primary and secondary dysmenorrhoea (Alonso and Coe 2001; Dorn *et al.* 2009). To address the lack of information about the impact of primary dysmenorrhoea on mood state, as part of the study reported in Chapter 2a, I investigate the mood of women with and without dysmenorrhoea during the painful menstruation phase as well as during the pain-free late-follicular and luteal phases of the menstrual cycle.

1.3.6.2 Sleep

Most studies have focused on the impact of dysmenorrhoeic pain on daytime functioning, with little attention paid to the impact of pain on sleep. The National Sleep Foundation's Women and Sleep Poll (1998) found that women reported more disturbed sleep during the first few days of menstruation than at other times of the menstrual cycle and that 28% of the sample reported that their sleep was disturbed by menstrual cramps or pain (NSF 1998). In association with their painful uterine cramps, women with dysmenorrhoea frequently complain of daytime fatigue and sleepiness; which further is suggestive of disturbed sleep (Delgado *et al.* 1994; Chen and Chen 2005; El-Gilany *et al.* 2005; Ohde *et al.* 2008). The following section provides an overview of how sleep is assessed and discusses the relationship between pain and sleep.

1.3.6.2.1 Assessment of Sleep

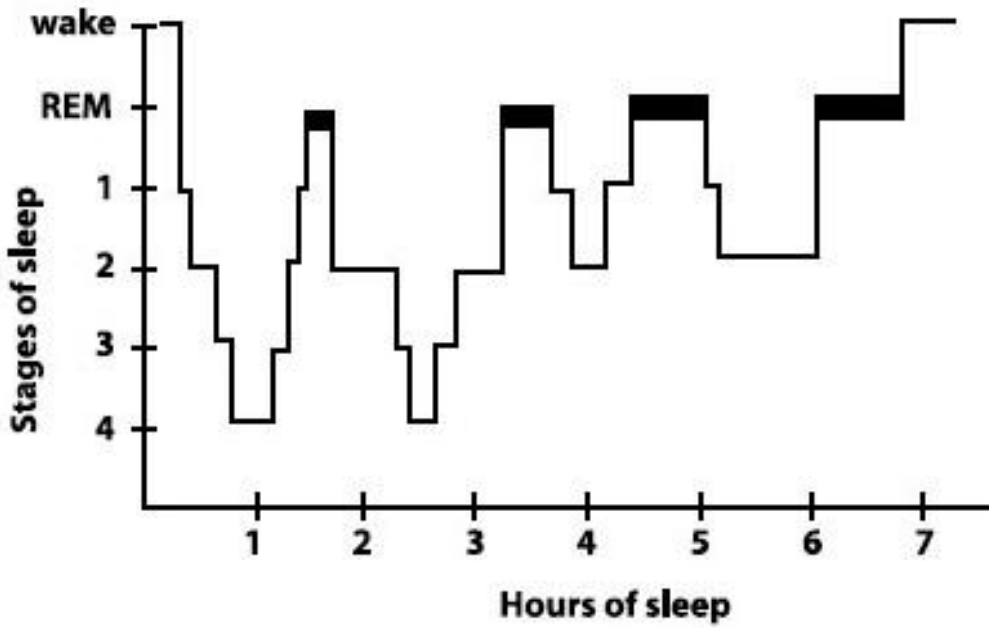
Sleep is a distinctive form of rest. It is an essential physiological and rhythmic state that is regulated by autonomic, homeostatic and circadian processes (Hirshkowitz 2004). The regulation of sleep is complex and beyond the scope of this review. Several substances are involved in the regulation of sleep, including GABA, adenosine, orexin, histamine, and PGs. For example, adenosine and PGD₂ are believed to be endogenous sleep-promoting substances (Roberts *et al.* 1980; Ueno *et al.* 1983; Pentreath *et al.* 1990; Islam *et al.* 1991; Pandey *et al.* 1995; Hayaishi 2002; Porkka-Heiskanen *et al.* 2002). Orexin A and PGE₂ generate arousal effects; by exciting the histaminergic tuberomammillary nucleus neurons, orexin A induces wakefulness (Eriksson *et al.* 2001) and PGE₂ is believed to be involved in the maintenance of the waking state (Matsumura *et al.* 1988; Onoe *et al.* 1992; Gerozissis *et al.* 1995).

Based on numerous physiological parameters, several types of sleep exist, each with specific characteristics, functions and regulatory mechanisms (Hirshkowitz 2004; Carskadon and Dement 2005). Polysomnography (PSG) allows for the objective assessment of sleep by measuring brain activity, eye activity and muscle activity using electroencephalography (EEG), electro-oculography (EOG) and electromyography (EMG), respectively (Carskadon and Dement 2005). Commonly used terms in PSG reports, as well as their definitions, as described by Spriggs (2002), are listed in Table 2 (Spriggs 2002).

Table 2. Common terms used in the analysis of polysomnographic recordings. Table 2 is generated using information from Spiggs, 2002 and Rechtschaffen and Kales, 1968.

PSG Terms	Definition
Lights Out	The beginning of the study, when the subject begins trying to fall asleep
Lights On	The end of the study - when the subject wakes up
Sleep Onset Latency (SOL)	The time it takes to fall asleep
Total Recording Time (TRT)	The duration from Lights Out to Lights On
Total Sleep Time (TST)	The amount of actual sleep time in a Sleep Period; equal to total recording time minus the sum of in-bed wakefulness and Total Movement Time
Wake after Sleep Onset (WASO)	The total amount of time spent awake after the onset of sleep
Movement Time (MT)	Time when the subject is moving and the channels are obscured for more than 15 seconds because of this movement
Arousal	An interruption of sleep continuity in which there is a shift in EEG frequency
Total Sleep Period	A period of time measured from Sleep Onset to final awakening. In addition to Total Sleep Time, it is comprised of the time taken up by Arousals and Movement Time
Sleep Efficiency (SE)	The percentage of the Total Recording Time that the subject was asleep ($SE = TST/TRT$)

Given that sleep stages are intervals of sleep with distinct EEG, EOG and EMG characteristics, polysomnographic records provide a means for the identification and differentiation between the various stages of sleep. The pattern or progression of the sleep stages throughout a sleep period is referred to as sleep architecture (Spriggs 2002). Figure 3 is an example of a hypnogram, which shows the distribution of sleep stages during the night.



According to the standard criteria proposed for sleep scoring (Rechtschaffen and Kales 1968), sleep can be divided broadly into two stages: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM sleep can be further divided into four sleep stages: Stages 1, 2, 3 and 4 (Rechtschaffen and Kales 1968). The depth of sleep progressively increases from Stage 1 through to Stage 4, and similarly arousal thresholds are normally lowest during Stage 1 sleep and gradually increase until they reach their highest levels in Stage 4 sleep (Roth and Roehrs 2000; Hirshkowitz 2004). Stage 1 is characterised by a low-voltage mixed-frequency EEG and is considered a transitional stage of sleep, as it has characteristics of both wakefulness and sleep (Hirshkowitz 2004). Stage 1 comprises 2-5% of total sleep time (TST) (Hirshkowitz 2004; Carskadon and Dement 2005). Stage 2 sleep is characterised by the presence of sleep spindles and K-complexes on the EEG, and comprises 45-55% of TST (Hirshkowitz 2004; Carskadon and Dement 2005). Stage 3 and 4 often are collectively referred to as slow wave sleep (SWS) or delta sleep, due to the characteristic presence of high amplitude, low frequency delta waves during these sleep stages (Hirshkowitz 2004; Carskadon and Dement 2005). SWS constitutes 13-23% of TST (Carskadon and Dement 2005). REM sleep constitutes 20-25% of TST (Hirshkowitz 2004; Carskadon and Dement 2005) and is defined by the presence of muscle atonia in the EMG, episodic bursts of rapid eye movements, and low amplitude, mixed frequency EEG (Roth and Roehrs 2000). Saw-tooth theta waves may also be present during REM sleep (Hirshkowitz 2004).

During a normal sleep period, NREM sleep and REM sleep alternate in 3-5 cycles, each lasting approximately 90 - 120 minutes (Hirshkowitz 2004). In general, SWS predominates in the first

third of the night, while REM sleep is the dominant sleep state during the second half of the sleep period (Hirshkowitz 2004).

Although PSG records allow for the continuous and objective assessment of an individual's sleep architecture and sleep efficiency over an entire sleep period, subjective sleep assessments using questionnaires and sleep diaries provide valuable information regarding an individual's perception of their sleep (Perlis *et al.* 1997; Baker *et al.* 1999b; Baker and Driver 2004), which does not always align with objective assessments. For example, perceived sleep quality may be affected by psychological state, which affects sleep appraisal processes rather than sleep itself (Krystal and Edinger 2008). It therefore is important for studies to include both subjective and objective assessments when investigating sleep.

1.3.6.2.2 Pain and Sleep

When one is in an awake, aroused and conscious state, pain is a combination of sensory perception and emotional evaluation (Bromm 1995). However, since sleep is a state of altered consciousness, one's sensitivity to external stimuli, including pain, is reduced when sleeping as sensory information is processed differently (Beydoun *et al.* 1993; Carskadon and Dement 2005).

Nevertheless, despite the reduction in cognitive and motor reactions to pain during sleep, painful stimuli during sleep have been found to elicit physiological reactions and, in fact, pain is a major disruptor of sleep (Menefee *et al.* 2000; Onen *et al.* 2005). Studies have evaluated

the effects of a variety of experimental pain stimuli during sleep on cerebral responses in healthy subjects. Muscle-pain stimuli have been shown to provoke an arousal effect, including reduced delta EEG activity and increased alpha 1 and beta activity (Drewes *et al.* 1997). Joint-pain stimuli have been found to provoke decreases in the lowest EEG frequency bands (delta, theta and alpha 1) and increases in the higher frequency EEG bands (alpha 2, sigma and beta). No differences were observed in the EEGs when cutaneous pain stimuli were applied (Drewes *et al.* 1997). Noxious thermal stimuli applied to healthy subjects have been shown to lead to awakenings from Stage 2 sleep, with higher intensities required to evoke arousal from SWS and REM sleep (Bentley *et al.* 2003). Similarly, hot stimuli have been shown to provoke a moderate level of cortical arousal during sleep, with more sleep arousals in the lighter Stage 2 sleep compared with SWS and REM sleep (Lavigne *et al.* 2000).

Epidemiological studies also suggest that a tight relationship exists between clinical pain and sleep disturbances (Pilowsky *et al.* 1985; Gislason and Almqvist 1987; Goodin *et al.* 2011). A large community health survey of 1765 participants revealed pain to be the variable that was most strongly correlated with sleep problems (Moffitt *et al.* 1991). Between 50% and 90% of patients with chronic pain conditions, such as arthritis, fibromyalgia and low back pain, complain of poor sleep in relation to their pain conditions (Lavigne *et al.* 2005). In fact, pain is believed to be the primary cause of insomnia in patients with various medical conditions (Drewes and Arendt-Nielsen 2001).

In addition to a high prevalence of subjective sleep disturbances, polysomnographic evidence confirms sleep disruptions in patients with various pain conditions, particularly

musculoskeletal disorders such as rheumatoid arthritis and fibromyalgia (Gislason and Almqvist 1987; Moffitt *et al.* 1991; Jennum *et al.* 1993; Drewes and Arendt-Nielsen 2001; Wolfe *et al.* 2006). Typically, pain reduces sleep efficiency and alters sleep architecture by increasing wakefulness and Stage 1 sleep, and by reducing SWS and REM sleep (Onen *et al.* 2005). In addition, patients with chronic pain have an increase in alpha activity during sleep; reflecting less restorative sleep (Wittig *et al.* 1982; Mahowald *et al.* 1989; Roizenblatt *et al.* 2001).

The relationship between sleep and pain is bidirectional. Just as pain impacts sleep, so too can a disturbed sleep impact on the sensation of pain. Indeed, numerous studies have determined a strong association between poor sleep and fatigue, excessive daytime sleepiness, stiffness and pain (Gislason and Almqvist 1987; Belza 1995; Stanton *et al.* 2006; Takahashi *et al.* 2006; Wolfe *et al.* 2006; Bennett *et al.* 2007). Even in healthy individuals, sleep disturbances or sleep deprivation have been found to accentuate pain or result in hyperalgesia (Onen *et al.* 2001; Azevedo *et al.* 2011; Goodin *et al.* 2011). A poorer sleep quality has been associated with pain catastrophisation of the cold pressor task (Goodin *et al.* 2011). Similarly, 40 hours of total sleep deprivation has been reported to result in hyperalgesia (Onen *et al.* 2001). On the other hand, rebound sleep, evident after sleep deprivation, generates an analgesic effect that is comparable to that achieved using acetaminophen or NSAIDs in healthy subjects (Onen *et al.* 2001).

In summary, the relationship between pain and sleep is reciprocal: painful stimuli (both clinical and experimental) disrupt sleep. Sleep deprivation or sleep disruption subsequently exacerbate

sensitivity to pain thereby intensifying the effects of the pain on daytime functioning (Onen *et al.* 2001; Ohayon 2006). The ultimate result is a vicious cycle in which sleep disturbance and pain ensure the maintenance and augmentation of each another.

1.3.6.2.3 Dysmenorrhoea and Sleep

Despite anecdotal reports of significantly poorer sleep quality in women with menstrual cramps, the only two studies that have investigated the extent to which dysmenorrhoeic pain disturbs subjective and objective measures of sleep, have conflicting results (Baker *et al.* 1999a; Araujo *et al.* 2011). Baker *et al.*, 1999, investigated the sleep architecture of ten women with unmedicated severe primary dysmenorrhoea and eight women free from any menstrual-associated disorders on the first night of menstruation as well as during the mid-follicular and mid-luteal phases of their menstrual cycles. In association with their pain, the dysmenorrhoeic women rated their sleep quality as significantly worse than controls during menstruation, and compared with their own pain-free follicular and luteal phases (Baker *et al.* 1999a). Sleep disturbances also were evident in PSG recordings; women with dysmenorrhoea had significantly reduced SE during menstruation, with an extended combined time spent awake, moving and in light Stage 1 sleep, compared with both the pain-free phases of their menstrual cycle, and with controls. While experiencing pain, women with dysmenorrhoea had significantly less REM sleep than when they were pain-free, however dysmenorrhoeic pain had no significant effect on SWS.

The second study reported quite the opposite; overnight PSG recordings of 24 women during menstruation (8 women without menstrual pain, 8 women experiencing menstrual pain without medication, and 8 women experiencing menstrual pain with medication), showed that the objective sleep of women experiencing menstrual pain was not significantly different to that of women without menstrual pain, or to that of women taking medication to relieve their menstrual pain (Araujo *et al.* 2011). Subjective sleep quality was not assessed. The main difference between the two studies is the severity of dysmenorrhoeic pain experienced by the two cohorts of women; the women in the study conducted by Araujo *et al.* (2011) reported mild-to-moderate menstrual pain, whereas those in the study by Baker *et al.* (1999a) reported severe menstrual pain. Furthermore, the mean age of the women with dysmenorrhoea who participated in the Araujo *et al.* (2011) study (mean $\pm$ SD of women without medication: 35 ± 7 years old and women with medication: 37 ± 7 years) was greater than that of those in the Baker *et al.* (1999a) study (23 ± 5 years); this difference may have been significant as only 5% of women above 35 years of age have been shown to experience severe menstrual pain (Polat *et al.* 2009). Therefore, it is likely that the women included in the more recent study did not experience menstrual pain severe enough to disrupt their sleep. Indeed, no woman reported being awakened during the night due to the pain (Araujo *et al.* 2011). In addition, no distinction was made between primary and secondary dysmenorrhoea, and women were only assessed once in a random menstrual cycle phase, with approximately 6% of women being assessed during the ovulatory phase, 38% during the follicular phase, 21% during the luteal phase, and 35% in an anovulatory menstrual cycle. Thus comparisons could not be made within the same women, with and without pain (Araujo *et al.* 2011).

As with other painful stimuli (discussed in Section 1.3.6.2.2), the uterine cramps, characteristic of dysmenorrhoea, may be the cause of a vicious cycle of negative events; menstrual pain reduces sleep quality and efficiency, and the consequent fatigue experienced by these women is likely to intensify the negative effect of the pain on daytime functioning and mood (Driver and Baker 1998). The finding from the study by Baker *et al.* (1999a) that primary dysmenorrhoea is associated with disturbed sleep leads to the question of whether alleviating dysmenorrhoeic pain will restore sleep architecture and improve sleep quality in women who suffer from this menstrual-associated disorder. Therefore, my study described in Chapter 5, investigates whether a readily available non-steroidal anti-inflammatory drug, diclofenac potassium, is effective in relieving night-time dysmenorrhoeic pain, and consequently restoring sleep quality in women with severe primary dysmenorrhoea.

1.3.7 Treatment of Primary Dysmenorrhoea

On account of the PG-based aetiology of primary dysmenorrhoea, the current most common pharmacological treatment for dysmenorrhoea is non-steroidal anti-inflammatory drugs (NSAIDs) (Harel 2004). NSAIDs are classified as prostaglandin synthetase inhibitors and are, on a global scale, among the most frequently prescribed group of drugs (Frolich 1997; Warner *et al.* 1999; Bianchi 2004). The various formulations of NSAIDs have comparable efficacy for dysmenorrhoea, and pain relief is successfully achieved in 64-100% of women (Smith 1993; Marjoribanks *et al.* 2003; Proctor and Farquhar 2006).

However, about 15% of women across the age range who suffer from dysmenorrhoea do not respond to, or are intolerant to PG-inhibitors (Rauh *et al.* 1985; Campbell and McGrath 1999). In these women, oral contraceptives often are used as second-line therapy. The synthetic hormones in oral contraceptives suppress ovulation and reduce the thickness of the endometrial lining of the uterus, thereby reducing the volume of menstrual fluid, PG synthesis and dysmenorrhoeic pain (Dawood 1995; Proctor *et al.* 2001; Ruoff and Lema 2003; Strowitzki *et al.* 2012). However, a recent meta-analysis has confirmed the long-suspected association between oral contraceptive use and the risk of venous thromboembolism (Manzoli *et al.* 2012). Hormonal intrauterine devices, which typically reduce bleeding, have also been shown to reduce the severity of menstrual pain (Suhonen *et al.* 2004; Lindh and Milsom 2013). However, the use of hormonal intrauterine devices in nulliparous women is still relatively low (Lindh and Milsom 2013; Ekelund *et al.* 2014).

Other currently available therapeutic approaches for the management of dysmenorrhoeic pain include: transcutaneous electric nerve stimulation, which alters the body's ability to receive or perceive pain signals; transdermal nitroglycerin patches, which inhibit uterine contractions; acupuncture/acupressure; and surgical interventions such as laparoscopic uterosacral nerve ablation surgery (Ruoff and Lema 2003; Jones 2004; Proctor and Farquhar 2006; Cho and Hwang 2010; Gharloghi *et al.* 2012). Such therapeutical approaches, however, are not considered to be effective enough to be widely used in clinical practice (Khan *et al.* 2012), and randomised control trials showing efficacy of such approaches are limited (Proctor and Farquhar 2006).

Many women also resort to alternative non-pharmacologic therapies to manage their menstrual discomfort, although these often are ineffective. Alternative approaches include heating pads for cramps, extra bed rest or sleep, physical exercise, meditation, aromatic oils, ginger root tea, salt water, increased calcium intake, increased vitamin D intake and various food sources such as beans, tofu and salmon (Campbell and McGrath 1999; Ogunfowokan and Babatunde 2010; Lasco *et al.* 2012; Ou *et al.* 2012).

While approximately 47-70% of university students use analgesics for pain relief (Cronje and Kritzinger 1991; Polat *et al.* 2009; Ortiz 2010), an estimated 30% of adolescents do not use over-the-counter medications to treat their menstrual pain and only approximately 18% use prescription medication (Wenzloff and Shimp 1984; Campbell and McGrath 1997; O'Connell *et al.* 2006), although the perceived effectiveness of pharmacological methods in the treatment of menstrual discomfort is superior to that of non-pharmacologic methods. In a questionnaire-based study of 289 female adolescent subjects, 98% of these adolescents reported using no less than one non-pharmacologic method to control menstrual discomfort. However, the mean perceived effectiveness of most non-pharmacologic methods was reported to be below 40% (Campbell and McGrath 1999).

The large variability in the perceived efficacy of the various non-pharmacologic strategies suggests that the efficacy of such methods is personal; one technique may provide relative pain relief for one adolescent, but may not provide the same perceived pain relief for others. However, some studies indicate that methods with a direct physiological impact, such as heat and exercise, are more effective than psychological-based methods, such as distraction

(Campbell and McGrath 1999) and may be as effective as some NSAIDs. For example, an abdominal heat wrap was found to be as effective as ibuprofen, and more effective than acetaminophen in relieving dysmenorrhoeic pain (Akin *et al.* 2001; Akin *et al.* 2004).

1.3.7.1 Dysmenorrhoea and NSAIDs

NSAIDs act by inhibiting the enzyme that catalyses the conversion of arachidonic acid to cyclic endoperoxides, namely cyclo-oxygenase (COX) (see Figure 2), which in turn inhibits the production of PGs (Warner *et al.* 1999; Ruoff and Lema 2003). Given that suppression of PG formation results in a reduction in uterine PG secretion and thus less vigorous uterine contractions, many NSAIDs provide effective relief from dysmenorrhoeic pain. Thus, NSAIDs alleviate primary dysmenorrhoeic pain predominantly through the suppression of endometrial PG synthesis (Dawood 1995).

The COX enzyme exists in two isoforms, namely COX-1 and COX-2, each with different prevalence and effects in various tissues (Frolich 1997; Warner *et al.* 1999). Several studies have recently suggested a third isoform of COX, named COX-3 (Frolich 1997; Warner *et al.* 1999; Langford and Evans 2002; Harel 2004). Cyclooxygenase-3 is believed to be a spliced variant of COX-1 that is highly expressed in the CNS, but little is known about its physiological role.

COX-1 is believed to be the predominantly constitutive form of the enzyme, which is expressed widely throughout the body, and responsible for the production of PGs with a variety

of regulatory and homeostatic functions such as platelet aggregation, fluid and electrolyte balance, and maintenance of the gastric mucosa (Frolich 1997; Warner *et al.* 1999). In contrast, although COX-2 is also expressed constitutively in several organs such as the brain, kidney and female reproductive tract, it is believed to be predominantly the inducible form of the COX enzyme. Levels of COX-2 are low at basal conditions, but are rapidly expressed in a variety of tissues and in response to numerous pathophysiological states. Thus, PGs produced through the metabolism of arachidonic acid by COX-2 are essential, for example, in both acute and chronic inflammation, as well as in hyperalgesia (Frolich 1997; Warner *et al.* 1999).

The fact that COX exists in two isoforms, each responsible for the production of PGs with different functions, provides an explanation for the various effects of NSAIDs; they prevent the pathological over-production of PGs via COX-2 which contributes to their therapeutic (anti-inflammatory, analgesic and anti-pyretic) effects, and they prevent the physiological formation of PGs via COX-1, which accounts for most of their side-effects. Consequently, the favourable effects of NSAIDs are associated with COX-2 inhibition, while their undesired side-effects are associated with inhibition of COX-1 (Warner *et al.* 1999).

The distinction between the different COX isoforms and their physiological and pathological effects has led to the pharmacological production of NSAIDs with different selectivity for the COX enzymes. Therefore, according to their inhibitory activity on COX-1 and COX-2, there are four broad groups of NSAIDs, namely, selective COX-1 inhibitors, nonselective COX inhibitors, selective COX-2 inhibitors and specific COX-2 inhibitors (Frolich 1997; Warner *et al.* 1999). Although the clinical profiles of the various NSAIDs are generally similar, there are

distinct differences in the pharmacokinetics, efficacy, tolerability and serious side-effect profiles that are often of therapeutic relevance (Frolich 1997; Warner *et al.* 1999; Langford and Evans 2002). Selective COX-1 inhibitors include ketoprofen and suprofen, and are capable of inhibiting both COX-1 and COX-2, but have a preference towards COX-1 inhibition. Nonselective COX inhibitors are capable of inhibiting both COX-1 and COX-2 with poor selectivity for either of the isoforms. Therefore, nonselective COX inhibitors have the potential to simultaneously inhibit fever, pain and inflammation, as well as the physiological PG-dependent functions; examples include diclofenac, naproxen, mefenamic acid and ibuprofen. Selective COX-2 inhibitors include celecoxib and meloxicam, and are capable of inhibiting both COX-1 and COX-2, but preferentially inhibit COX-2. Specific COX-2 inhibitors are able to strongly inhibit COX-2 with only weak activity against COX-1; examples include rofecoxib and valdecoxib (Frolich 1997; Warner *et al.* 1999).

Specific COX-2 inhibitors were produced mainly because of concern over the gastrointestinal (GI) safety of traditional nonselective NSAIDs. Specific COX-2 inhibitors (coxibs) were therefore developed to provide the analgesic and anti-inflammatory properties of nonselective NSAIDs, while avoiding the GI complications associated with the inhibition of COX-1 (McQuay and Moore 2003; Ruoff and Lema 2003). While showing promise in the treatment of painful syndromes, including dysmenorrhoea, the cardiovascular safety of coxibs remains uncertain, and thus in many countries, these drugs have been withdrawn (McQuay and Moore 2003; Proctor and Farquhar 2006).

Several placebo-controlled studies have been conducted to test the effectiveness of nonselective NSAIDs, in particular, in the treatment of dysmenorrhoea. A meta-analysis of 31 studies on the efficacy of NSAIDs in primary dysmenorrhoea revealed that compared to placebo, naproxen, ibuprofen and mefenamic acid all provided significant pain relief (Zhang and Li Wan Po 1998). In addition, nonselective COX inhibitors reduced both the levels of $\text{PGF}_{2\alpha}$ and pain in small numbers of dysmenorrhoeic women (Chan and Dawood 1980). Substantiating these findings, subsequent studies performed on larger sample sizes, in a randomised, placebo-controlled manner, have found that nonselective COX inhibitor drugs, including diclofenac, zomepirac sodium, mefenamic acid, naproxen sodium, ketoprofen and ibuprofen, all are effective in the treatment of primary dysmenorrhoea (Harel 2004).

Effects of NSAIDs are generally tolerable, and GI safety issues are generally of less concern in acute use of NSAIDs compared to chronic use (Langford and Evans 2002). In addition, NSAIDs associated with the greatest GI toxicity have the highest selectivity for COX-1. The non-selective NSAID, diclofenac, while capable of producing full inhibition of both COX-1 and COX-2, has relatively poor selectivity for COX-1 (more than 4-fold selective for COX-2) (Warner *et al.* 1999). Consequently, diclofenac appears to be a safe option for the treatment of the acute pain experienced monthly by women with dysmenorrhoea.

1.3.7.1.1 Dysmenorrhoea and Diclofenac

Diclofenac is a phenylacetic acid derivative that is believed to be one of the most potent inhibitors of PG synthesis (Brogden *et al.* 1980). It has anti-inflammatory, antipyretic and analgesic effects (Riihiluoma *et al.* 1981). The pharmacological properties of diclofenac allow it to exert an extended duration of action, despite its rapid systemic elimination, as illustrated by its short half-life of approximately 2 hours. The favourable side effect profile of diclofenac also may be explained by these properties (Brogden *et al.* 1980; O'Brien W 1986).

Indeed, diclofenac has been reported to have a low incidence of GI side-effects (Frolich 1997). In an extensive review of over 100 000 patients treated with diclofenac worldwide, the incidence of side-effects was found to be 12%. The most frequent side-effects were those involving the GI tract, such as nausea and vomiting, followed less frequently by CNS symptoms such as drowsiness (Willkens 1985). When Warner *et al.* (1999), ranked twelve drugs from least to most damaging in terms of GI toxicity, ibuprofen and diclofenac were ranked as the least and second least harmful drugs respectively (Warner *et al.* 1999).

Several studies have shown that diclofenac is effective at alleviating day-time dysmenorrhoeic pain. Diclofenac was found to be more effective than placebo in the treatment of 28 women with primary dysmenorrhoea (Ingemanson *et al.* 1981). Similarly, when low doses of diclofenac sodium (75 mg daily) were used to treat 35 women with dysmenorrhoea, not only was diclofenac effective in significantly reducing menstrual pain compared to placebo, but it also resulted in a significant decline in the amount of menstrual bleeding (Riihiluoma *et al.* 1981). Chantler *et al.* (2008) found that 50 mg of diclofenac provided complete relief from

dysmenorrhoeic pain; described by the authors as a reduction in pain that was not significantly different from 100% (Chantler *et al.* 2008). In addition, aceclofenac, a glycolic acid ester of diclofenac (Hinz *et al.* 2003), used either alone (Letzel *et al.* 2006), or in combination with drotaverine (a smooth muscle relaxant) (Pareek *et al.* 2010), has been reported as a safe and well-tolerated analgesic for primary dysmenorrhoea. Diclofenac has additionally been shown to restore dysmenorrhoeic pain-induced reduction in physical activities, such as walking and bending (Chantler *et al.* 2009b).

However, although diclofenac has been identified as an effective treatment for dysmenorrhoea in the short-term, from two to eight hours after treatment administration (Marchini *et al.* 1995; Facchinetti *et al.* 2002; Chantler *et al.* 2009b), the daily doses used in each study varied considerably (from one to six times daily) (Riihiluoma *et al.* 1981; Marchini *et al.* 1995; Facchinetti *et al.* 2002; Chantler *et al.* 2008; Chantler *et al.* 2009b), with most studies allowing participants to choose their own dosing schedule based on the need for pain relief (Riihiluoma *et al.* 1981; Marchini *et al.* 1995; Facchinetti *et al.* 2002; Chantler *et al.* 2008). To my knowledge, only one study has monitored dysmenorrhoeic pain severity over a period of more than 8 hours with diclofenac potassium versus placebo (Chantler *et al.* 2008). In this study, pain intensity was measured before and 2 hours after treatment (diclofenac, refecoxib, meloxicam or placebo) over a 2-to-3-day period. However, dosages again were not consistent among women, as each woman was allowed to self-medicate with up to two pills daily (Chantler *et al.* 2008). Therefore, there still is a need to monitor menstrual pain intensity over longer periods of time. In addition, most research on the use of diclofenac for the treatment of dysmenorrhea has used diclofenac sodium, and not diclofenac potassium. Although

pharmacokinetic studies show similar bioavailability between diclofenac sodium and potassium, the mean time to reach maximal plasma levels is shorter with diclofenac potassium (± 30 minutes) (Moore 2007) compared with diclofenac sodium (± 1.5 to 2 hours) (Brogden *et al.* 1980). Such properties may explain a faster onset of action with diclofenac potassium (Bakshi *et al.* 1992). My study in Chapter 4 therefore investigates the progression of menstrual pain in women with severe primary dysmenorrhoea over a 24-hour period, both when taking placebo, and when medicated with the daily recommended dose of diclofenac potassium taken at prescribed time-points.

Furthermore, although diclofenac has been shown to be effective in treating day-time dysmenorrhoeic pain, to my knowledge, no studies have assessed the efficacy of diclofenac in alleviating night-time menstrual pain. Therefore, my study in Chapter 5 investigates whether diclofenac potassium, compared to placebo, effectively relieves night-time pain and restores sleep quality in women with severe primary dysmenorrhoea.

1.4 AIMS

Figure 4 represents a conceptual framework showing the gaps in the literature that are addressed in this thesis.

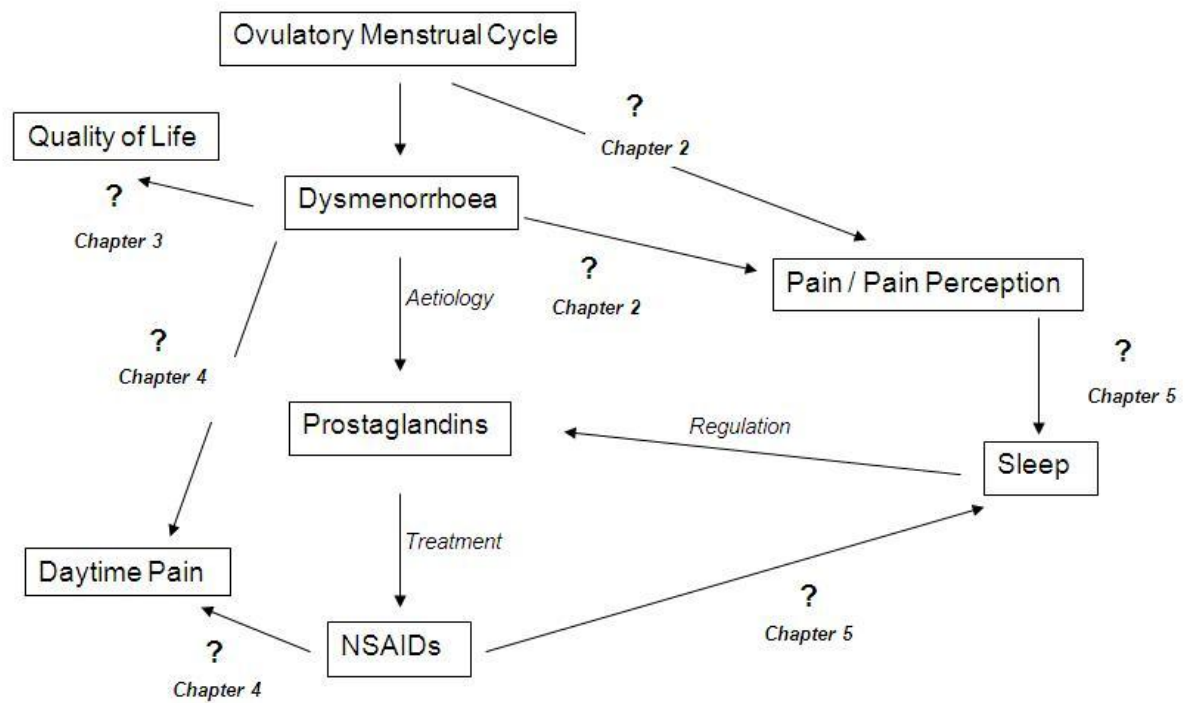


Figure 4. A conceptual framework summarising the topics discussed, as well as the missing links highlighted in the introduction of this thesis.

The literature is still conflicting as to whether women with primary dysmenorrhoea are hypersensitive to painful stimuli. The research aims presented in Chapter 2, therefore, were to determine whether:

- 1) Women with a history of severe primary dysmenorrhoea, compared to women without dysmenorrhoea, have increased sensitivity to deep-muscle pain induced by hypertonic saline injection both within and outside the areas of referred menstrual pain (Chapter 2a).
- 2) Menstrual cycle phase affects the perception of pain in women with a history of severe primary dysmenorrhoea, compared to women without dysmenorrhoea (Chapter 2a).
- 3) Women with a history of severe primary dysmenorrhoea, compared to women without dysmenorrhoea, have increased sensitivity to ischaemic-muscle pain in an area outside of referred menstrual pain (forearm), during the painful menstruation phase and during the pain-free follicular phase (Chapter 2b).

A secondary aim of Chapter 2a was to investigate:

- 4) Mood in women with and without primary dysmenorrhoea at different phases of the menstrual cycle.

The pain experienced by women with primary dysmenorrhoea has been described as intense and debilitating and, as such, has been shown to have a detrimental effect on day-time functioning and physical activity. However, surprisingly, very little is known about the effect of primary dysmenorrhoeic pain specifically on quality of life. Therefore the aim of Chapter 3 was to:

- 5) Assess the quality of life in women with a history of severe primary dysmenorrhoea, compared to women without dysmenorrhoea, during menstruation and during a pain-free phase of the menstrual cycle.

Beyond understanding the aetiology and impact of primary dysmenorrhoea, it is also imperative to investigate effective treatment of the pain. Little is known about the efficacy of diclofenac potassium in alleviating menstrual pain beyond 8 hours. Also, no study, to my knowledge, has investigated the effectiveness of diclofenac potassium in relieving night-time pain and in potentially restoring sleep quality in women with severe primary dysmenorrhoea. The research aim of Chapter 4 was to:

- 6) Assess the efficacy of the daily recommended dose of diclofenac potassium, compared to placebo, in alleviating menstrual pain across a 24-hour time period in women with a history of severe primary dysmenorrhoea.

The aim of Chapter 5 was to determine:

- 7) Whether objective and subjective measures of sleep quality are impaired by primary dysmenorrhoeic pain.
- 8) The effectiveness of diclofenac potassium, compared to placebo, in alleviating night-time dysmenorrhoeic pain and restoring objective sleep architecture and perceived sleep quality in women with severe primary dysmenorrhoea.

CHAPTER TWOa

Paper 1:

Women with Dysmenorrhoea are Hypersensitive to Experimental Deep Muscle Pain across the Menstrual Cycle

Women With Dysmenorrhea Are Hypersensitive to Experimental Deep Muscle Pain Across the Menstrual Cycle

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Abstract: Primary dysmenorrhea is a common painful condition in women that recurs every month across the reproductive years. The recurrent nociceptive input into the central nervous system that occurs during menstruation each month in women with dysmenorrhea is hypothesized to lead to increased sensitivity to painful stimuli. We investigated whether women with primary dysmenorrhea are hyperalgesic to deep muscle pain induced by a cleanly nociceptive method of hypertonic saline injection. Pain stimulation was applied both within an area of referred menstrual pain (lower back) and at a remote site outside of referred menstrual pain (forearm) in 12 healthy women with severe dysmenorrhea and 9 healthy women without dysmenorrhea, at 3 phases of the menstrual cycle: menstruation and follicular and luteal phases. Women rated their pain severity on a 100-mm visual analog scale every 30 seconds after injection until the pain subsided. In both groups of women, menstrual cycle phase had no effect on the reported intensity and duration of muscle pain. However, women with dysmenorrhea had increased sensitivity to experimental muscle pain both at the site of referred pain and at a remote nonpainful site, as assessed by peak pain severity visual analog scale rating, area under the visual analog scale curve, and pain duration, compared to women without dysmenorrhea. These data show that women with severe primary dysmenorrhea, who experience monthly menstrual pain, are hyperalgesic to deep muscle pain compared to women without dysmenorrhea.

Perspective: Our findings that dysmenorrheic women are hyperalgesic to a clinically relevant, deep muscle pain in areas within and outside of referred menstrual pain indicates lasting changes in pain sensitivity outside of the painful period during menstruation.

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Key words: Dysmenorrhea, pain sensitivity, muscle hyperalgesia, menstrual cycle.

Primary dysmenorrhea, defined as painful menstrual cramps of uterine origin in the absence of pelvic pathology, is the most common gynecologic condition among women of reproductive age.^{11,35,55} Recurrent nociceptor inputs are known, in some circumstances, to

alter the processing of pain within the central nervous system.^{37,75} Thus, repeated exposure to painful menstrual cramps is hypothesized to cause functional and structural alterations throughout the central nervous system, resulting in central sensitization and, hence, increased sensitivity to pain.^{8,10,22,28,46,68,69,74,76}

Indeed, recent studies have demonstrated significant differences in the central nervous system between otherwise healthy women who experience moderate-to-severe dysmenorrheic pain and healthy women without dysmenorrhea. Such differences are evident in cerebral activity induced by noxious skin stimulation,⁷⁴ cerebral metabolism,⁶⁹ and cerebral structure.⁶⁸ Although the functional consequences of these central changes are unclear, volume changes in the gray matter of regions involved in pain modulation in women with

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dysmenorrhea may underlie a combination of impaired pain inhibition and amplified pain facilitation,⁶⁸ possibly making them more sensitive to painful stimuli compared to women without dysmenorrhea.

Several studies have investigated pain perception between women with and without dysmenorrhea, but the results are inconsistent. Some studies report that women with dysmenorrhea have enhanced responses to experimental noxious stimuli, such as heat pain, pressure pain, laser pain-evoked potentials, and electrical pain stimuli applied to the abdomen, lower back, and extremities.^{8,22,26,28,32,74} Others report no differences in the perception of experimental pain (including ischemic pain, cold pressor pain, heat pain, electrical stimulation of the skin) between dysmenorrheic and nondysmenorrheic women.^{1,3,33} The inconclusive results have been attributed to variations in experimental protocols; noxious stimuli, depth and site of pain stimulation, pain assessment procedures, and definition of menstrual cycle phase vary markedly across experiments.^{22,60}

In particular, depth of noxious stimulation is critical because muscles are more likely to become hyperalgesic under recurrent visceral pain conditions like dysmenorrhea than are subcutaneous tissues and skin.^{23,71} Indeed, the only study that compared superficial and deep pain sensations in muscle found that women with dysmenorrhea were hyperalgesic in muscle but not skin compared to controls, particularly perimenstrually.²² However, this study used electrical stimulation, which has been criticized as a method of experimental pain induction as it activates both nociceptive and nonnociceptive fibers, hence producing both painful and nonpainful sensations.²⁷ Electrical stimulation is also confounded by concurrent activated muscle twitches,⁵ and it evokes pain sensations that are less natural than other pain stimuli.^{19,27} Intramuscular injection of hypertonic saline provides a better nociceptive and more clinically relevant method of inducing deep muscle pain,^{29,38,40,63} causing a mild, acute muscular pain that closely mimics clinical musculoskeletal pain both in subjectively perceived quality and in its effects on motor performance.⁶

In this study, we investigated whether women with severe dysmenorrhea are hyperalgesic to deep muscle pain, induced by hypertonic saline, compared to women without dysmenorrhea. Because there is controversy in the literature as to whether or not pain sensitivity differs in women with^{3,8,22,26,28,33,74} and without dysmenorrhea^{3,8,15,17,18,22,25,26,28,33,34,36,39,41-45,53,54,56,57,59,61,62,64,66,72,74} as a function of menstrual cycle phase, we investigated responses at 3 hormonally distinct phases of the menstrual cycle. Finally, to assess whether sensitization of muscle is specific to the area of referred menstrual pain, we induced deep muscle pain stimulation in 2 different muscle groups: the lower back, within the area of menstrual pain referral, and the forearm, outside the area of menstrual pain referral. We hypothesized that women with dysmenorrhea would be hyperalgesic to deep muscle pain compared to women without dysmenorrhea in areas inside and outside the

area of menstrual pain referral in the menstruation, follicular, and luteal phases of the menstrual cycle.

Methods

Subject Recruitment

Healthy women aged between 18 and 30 years were asked to volunteer for the study. Initially, all volunteers were interviewed and screened with questionnaires to ensure that they were generally healthy and met all of the inclusion criteria of the study. The women were required to be nulliparous, have regular menstrual cycles between 22 and 35 days in length, and not have been taking any form of hormonal contraception for at least 6 months before the study. Volunteers were required to score less than 6 on the 30-item version of the General Health Questionnaire, indicating normal psychological status.²⁴ In addition, volunteers were excluded from the study if they had severe premenstrual syndrome (PMS)²⁰; if they had any chronic illness, such as diabetes; and if they were taking any long-term medication, including pain medication (analgesic or anti-inflammatory), more than once a week. Furthermore, the women were required to not have any clinical musculoskeletal disorders or any palpable trigger points in their lower back and arms.

Women were then allocated to either the primary "dysmenorrheic" or "non-dysmenorrheic/control" group, based on the intensity of their monthly menstrual pain. To be included in the dysmenorrheic group, women had to have a history of dysmenorrhea starting shortly after menarche¹¹ and were required to have "severe" menstrual pain every month for the past 6 months that necessitated use of pain-relieving medications. Women were asked to assess the intensity of their menstrual pain over the last 6 months on a 100-mm visual analog scale (VAS) anchored from "no pain at all" to "the worst pain I have ever felt." VAS scores were obtained by measuring the distance, in millimeters, from the beginning anchor point ("no pain at all") to the mark filled in by the subjects. Women who rated their menstrual pain higher than 60 mm on the VAS were considered to have severe dysmenorrheic pain.¹² In contrast, women were included in the control group if they rated their menstrual pain as less than 30 mm on the VAS.

Fourteen healthy women with a history of primary dysmenorrhea and 10 healthy women without a history of dysmenorrhea agreed to participate in the study and gave written informed consent before participation. Ethical clearance was obtained from the University of the Witwatersrand's Committee for Research on Human Subjects, which adheres to the principles of the Declaration of Helsinki (Clearance no. M080627). Both groups of women completed identical procedures.

Screening Phase

All women underwent a 1-month screening phase to confirm whether or not they had severe primary dysmenorrhea, had ovulatory menstrual cycles, and did not have PMS. Every evening during the month-long screening

period, the women completed the Penn Daily Symptom Report,²⁰ a validated daily symptom rating to evaluate symptoms of PMS. A score of 80 or greater in the late-luteal phase, with an increase of more than 50% from the postmenstrual score, reflects severe PMS.²⁰ None of the women in the study met these criteria.

Every evening during the menstruation phase of the screening month, the women evaluated the intensity of their dysmenorrheic pain experienced during the course of the day by completing a VAS for pain. To qualify for the experimental phase of the study, the women needed to rate their menstrual pain either above 60 mm for at least 1 day during the screening phase (forming the "dysmenorrheic" group), or less than 30 mm on the VAS for all the days of menstruation (forming the "control" group). In addition, during this 1-month screening period, all the women used a commercially available self-test ovulatory kit that detects the presence of luteinizing hormone in urine (Clearplan Easy, Unipath Diagnostics, Bedford, United Kingdom) to confirm that they had ovulatory menstrual cycles.

Following screening, 2 women with dysmenorrhea and 1 control were excluded from further participation. One woman with dysmenorrhea commenced hormonal contraception and another was suspected to have pain secondary to pelvic pathology, and a woman in the control group developed an irregular menstrual cycle. Twelve women with severe primary dysmenorrhea and 9 controls therefore completed the study.

Experimental Phase

Participants were tested at 3 hormonally distinct phases of the menstrual cycle: menstruation phase (days 1–2), follicular phase (days 11–13), and luteal phase (days 17–22), where day 1 refers to the first day of menstruation. Women completed each experimental session between 1200 and 1400 hours on a single day during each of these 3 phases. The order of the experimental sessions was randomized in both groups of women, and all 3 sessions were completed within 1 menstrual cycle.

The women were asked to refrain from taking any medication, including pain-relieving medication for menstrual pain, on the day of the experiments. One dysmenorrheic woman chose to take rescue medication (ibuprofen 200 mg) for her menstrual pain 6 hours before her experimental session. Given the relatively short half-life of ibuprofen (approximately 2 hours), and the fact that when the woman came in to do the experiment she was experiencing severe dysmenorrheic pain (61 mm),¹² her data were included in the analysis.

Subjective Assessments of Mood and Dysmenorrheic Pain

To assess mood, at the beginning of each experimental session, the women completed the validated Profile of Mood States (POMS) questionnaire. The POMS is a validated questionnaire consisting of 65 questions that measure 6 identifiable mood or affective states: Tension-Anxiety; Depression-Dejection; Anger-Hostility;

Dysmenorrheic Women Are Hyperalgesic to Muscle Pain

Vigor-Activity; Fatigue-Inertia; and Confusion-Bewilderment.⁴⁶ A total mood score for each subject was calculated from the POMS by summing the negative mood scores, subtracting the vigor score, and adding a constant of 100 to avoid negative scores.⁵⁰ In addition, at the start of the experimental session during the menstruation phase, the women rated the intensity of their current menstrual pain on the 100-mm VAS anchored from "no pain" to "the worst pain I have ever experienced."

Hormone Assessment

To ensure that the women were in the correct menstrual cycle phase, 5 mL of venous blood was drawn by venous puncture from the brachial vein of each woman during each of the 3 menstrual phases. Serum was immediately separated from cells by centrifugation for 10 minutes at 1,300 rpm and stored at -70°C until assayed according to the manufacturer's instructions. Levels of progesterone and estradiol were determined using the Bayer ADVIA Centaur assay (Bayer Corp, Tarrytown, NY), a competitive immunoassay using direct chemiluminescent technology. The minimum detectable levels were 25.7 pmol/L and .48 nmol/L, respectively, for estradiol and progesterone. The maximum concentrations for the assay ranges were 3,670 pmol/L of estradiol and 190.8 nmol/L of progesterone. The intra- and interassay coefficients of variation were as follows: estradiol, 8.3 and 5.6%; progesterone, 5.3 and 3.6%, respectively.

Experimental Deep-Tissue Muscle Pain

On each visit, experimental muscle pain was induced in 2 distinct muscle groups: the erector spinae muscle and the extensor muscles of the forearm. The erector spinae muscle, at the lumbar level (L4/L5) of the lower back, was chosen as the muscle within the area of referred menstrual pain, and the forearm extensor muscle group was chosen as the muscle group outside the area of referred menstrual pain. In order to locate the extensor muscles of the forearm, the woman was seated resting her arm, in a pronated position, on an examination table next to the seat. Two thirds of the distance from the styloid process of the ulna to the lateral condyle of the radius was measured, and the belly of the muscle was located after asking the woman to extend her wrist. The erector spinae muscle was located by having the woman lie prone on an examination table and the left and right iliac crests were located by palpation. The spinous process of L4 was then located at the level of the iliac crests. The woman was then asked to hyperextend her back, and the belly of the erector spinae muscle was located on either side of the spinal column.

The side of the body (left or right) and the site (forearm or back) used to induce pain were randomized for each experimental session, and the second injection commenced only once the pain from the first injection had completely subsided. In order to remove any superficial pain due to the injection itself, a topical anesthetic cream (lignocaine 2.5%, prilocaine 2.5%) was applied at least 45 minutes before the experimental session to the overlying skin of the site at which the noxious stimulus was to be applied.

Deep muscle pain was induced by a .5 mL intramuscular injection of 5% sterile hypertonic saline.³⁰ A sterile 23-gauge, 25-mm needle was used to insert .5 mL of 5% sterile hypertonic saline at a depth of 1.5 cm into the erector spinae muscle, and a sterile 25-gauge, 16-mm needle was used to insert .5 mL of 5% sterile hypertonic saline at a depth of .5 cm into the extensor muscle of the forearm. All injections were administered by a medical doctor as a bolus over a maximum of 10 seconds and the needle was removed at the completion of the injection.

Immediately before each injection, and then every 30 seconds after the injection, until the pain had completely subsided, the women were asked to rate the intensity of their muscle pain on a 100-mm VAS anchored at "no pain" and "worst pain ever felt."

Statistical Analyses

All data were analyzed using STATISTICA (version 5; StatSoft, Tulsa, OK). A 2-tailed probability of $P \leq .05$ was considered to be statistically significant. All parametric values are expressed as mean $\pm$ standard deviation (SD), whereas all nonparametric values are expressed as medians (lower, upper 95% confidence limits).

All VAS measurements (in mm) used to describe dysmenorrheic and experimental muscle pain were normalized before statistical analyses using the arcsine transformation, as advised when a large number of values fall within the extremes of the scale.¹⁶ However, all text and graphs report the VAS data as back-transformed values (in mm). Three measures of pain intensity were derived from the VAS ratings following the injection of hypertonic saline: peak VAS, pain duration, and area under the VAS-time curve (AUC, $\text{mm} \cdot \text{s}^{-1}$). Peak VAS was the maximum VAS rating, in millimeters, used to describe the peak muscle pain. Pain duration was calculated as the total time, in seconds, from the time of injection until the pain had completely subsided. Lastly, to calculate AUC, an indicator of overall pain intensity,⁴⁸ the transformed VAS scores for each subject from the time of injection (time 0) until the pain had completely subsided were plotted on separate graphs, and best-fit curves were fitted (Table

curve 2D, version 3 for Win 32; Jandel Scientific Software, AISN Software Inc, San Rafael, CA). As is done consistently in the literature, we report all 3 of these measures: peak VAS (mm), pain duration (seconds), and AUC ($\text{mm} \cdot \text{s}^{-1}$). As expected, AUC correlated significantly with peak pain and duration of pain ($r > .6$, $P < .05$), and these variable are thus not independent.

Student unpaired t-tests were used to compare the demographic variables (age, anthropometric variables, and menstrual history), as well as menstrual pain intensity (VAS, mm) and hormone concentrations (progesterone and estradiol), between the 2 groups of women.

Mood (POMS scores) and VAS measurements (peak pain, duration of pain, and AUC) were analyzed according to group (dysmenorrheics and controls) and menstrual cycle phase (menstruation, follicular, and luteal) using 2-way repeated-measures analyses of variance (ANOVAs). Where appropriate, the Student-Newman-Keuls (SNK) post hoc test was used to assess the origin of any significant differences detected by the ANOVA models.

Results

Subject Characteristics

Characteristics of the 12 women with dysmenorrhea and the 9 control women without dysmenorrhea who participated in the experiment are shown in Table 1. Unpaired t-tests confirmed that the 2 groups of women were well matched for age, anthropometric variables, and menstrual history and that the women with dysmenorrhea had significantly more menstrual pain than the control group. Hormonal assays confirmed that each woman had ovulated and was in the correct menstrual cycle phase during the time of experimentation (Table 2). There were no differences between the dysmenorrheics and controls for either hormone level at any phase of the menstrual cycle.

Menstrual Pain Severity

During the menstruation phase, women with dysmenorrhea experienced significantly more menstrual pain at

Table 1. Characteristics of the Women Who Participated in the Study

	WOMEN WITH DYSMENORRHEA (N = 12)	CONTROL WOMEN (N = 9)	P VALUE (UNPAIRED 2-TAIL, T-TEST)
Age (years)	21 $\pm$ 2	22 $\pm$ 2	.33
Weight (kg)	59.2 $\pm$ 13.0	60.7 $\pm$ 12.7	.81
Height (m)	1.61 $\pm$.07	1.61 $\pm$.04	.94
Body mass index (kg/m^2)	22.7 $\pm$ 3.8	23.2 $\pm$ 4.0	.77
General Health Questionnaire score	2 $\pm$ 1	1 $\pm$ 2	.20
Age of onset of menses (years)	13 $\pm$ 2	14 $\pm$ 1	.21
Age of onset of dysmenorrhea (years)	14 $\pm$ 2	—	N/A
Number of years of menstruation	9 $\pm$ 3	9 $\pm$ 2	.94
Usual menstrual cycle length (days)	28 $\pm$ 0	28 $\pm$ 1	.18
Usual menstruation phase length (days)	5 $\pm$ 1	4 $\pm$ 1	.23
Average menstrual pain intensity (for previous 6 months; VAS, mm)	82 $\pm$ 12	4 $\pm$ 7	<.0001*

Abbreviation: N/A, not applicable.

NOTE. Data are expressed as mean $\pm$ SD.

*Significant difference between the dysmenorrheic and control groups.

Table 2. Progesterone and Estradiol Concentrations in the Women With Dysmenorrhea and the Control Women in the 3 Menstrual Cycle Phases

	NORMAL RANGES*		WOMEN WITH DYSMENORRHEA (N = 12)		CONTROL WOMEN (N = 9)		P VALUE (UNPAIRED 2-TAIL, T-TEST)	
MENSTRUAL CYCLE PHASE	PRGE (NMOL/L)	E ₂ (PMOL/L)	PRGE (NMOL/L)	E ₂ (PMOL/L)	PRGE (NMOL/L)	E ₂ (PMOL/L)	PRGE	E ₂
Menstruation	.5–4.5	69.4–905.4	2.4 ± .4	121.2 ± 34.9	2.1 ± .2	115.9 ± 44.9	.29	.76
Follicular	.5–4.5	130.3–2094.8	2.3 ± .5	435.8 ± 278.3	2.2 ± .3	524.3 ± 372.4	.61	.54
Luteal	10.6–89.1	82.2–939.5	38.8 ± 19.6	419.8 ± 214.6	32.8 ± 16.6	575.0 ± 217.4	.47	.12

Abbreviations: PRGE, progesterone; E₂, estradiol.

NOTE. Data are expressed as mean ± SD. P values are for comparisons between dysmenorrheics and controls' hormone values in each menstrual cycle phase.

*Bayer Diagnostics ADVIA Centaur Progesterone and Estradiol-6 III Assay Manuals.

the time of the experiment compared to controls: VAS scores (mean ± SD): 55 ± 19 mm versus 1 ± 2 mm; unpaired 2-tailed t-test: $t(19) = 8.29$, $P < .0001$. Seven of the 12 dysmenorrheic women experienced severe menstrual pain (>60 mm) at the start of the experimental session (1200 hours). The remaining 5 women reported severe pain in the morning of the experimental day but had moderate pain (>30 mm) at the start of the experiment. We ran exploratory analyses with unpaired t-tests to determine whether ratings of experimental pain differed between dysmenorrheic women with severe menstrual pain compared to dysmenorrheic women with moderate menstrual pain at the time of the experiment. There were no significant differences in any variables and the data were therefore pooled for all subsequent analyses.

Mood

The main effects of group ($F[1, 19] = 1.32$, $P = .3$) and phase ($F[2, 38] = .79$, $P = .5$) for total POMS scores were not significant. However, there was a significant group-phase interaction effect ($F[2, 38] = 4.53$, $P = .02$) (Fig 1). Women with dysmenorrhea had a significantly higher POMS total mood score, reflecting a poorer mood during the menstruation phase of

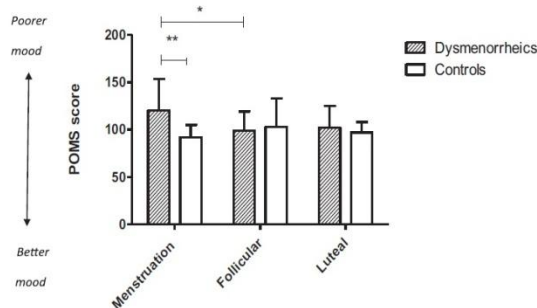


Figure 1. Changes in mood across the menstrual cycle in women with dysmenorrhea ($n = 12$) compared to women without dysmenorrhea ($n = 9$), as measured by the POMS questionnaire.⁴⁶ Data are expressed as mean ± SD. A 2-way repeated-measures analysis of variance was used to assess for a main effect of group and phase, and Neuman-Keuls post hoc tests determined the origin of significant differences. * $P < .05$, ** $P < .01$.

their cycle compared to controls ($P = .01$) and compared to their own pain-free follicular phase ($P = .05$).

Hypertonic Saline Injections

VAS profiles every 30 seconds from the time of injection ($t = 0$) until the pain subsided, for each of the 12 dysmenorrheic women, as well as the mean plot for the control group ($n = 9$) are illustrated in Fig 2. For both sites (lower back and arm) and across all menstrual phases, the control group generally rated the same painful stimulus as consistently lower in intensity and for a shorter duration than that reported in the dysmenorrheic women, as confirmed with statistical analyses described below.

Lower Back

Intramuscular injection of hypertonic saline into the lower back (Fig 3) produced significantly higher pain scores (measured by VAS scores) in the dysmenorrheic women compared to controls for peak pain (group effect: $F[1, 19] = 8.4$, $P = .009$); total duration of muscle pain (group effect: $F[1, 19] = 9.4$, $P = .006$); and AUC (group effect: $F[1, 19] = 6.3$, $P = .02$). There were no differences across the menstrual cycle in either group of women (phase effect for peak VAS: $F[2, 38] = .4$, $P = .7$; phase effect for total pain duration: $F[2, 38] = .2$, $P = .8$; phase effect for AUC: $F[2, 38] = .6$, $P = .5$). There were also no significant group-phase interaction effects for peak VAS ($F[2, 38] = .9$, $P = .4$), pain duration ($F[2, 38] = .04$, $P = 1.0$), and AUC ($F[2, 38] = 1.2$, $P = .3$) for muscle pain in the lower back. As shown in Fig 3, post hoc comparisons revealed that dysmenorrheic women had significantly more severe pain based on peak VAS, pain duration, and AUC than controls in the menstruation and luteal phases (SNK: $P < .05$). In the follicular phase, dysmenorrheic women had significantly greater pain duration (SNK: $P < .05$) and tended to have a greater peak VAS and AUC (SNK: $P < .1$) than controls.

Forearm

The intramuscular injection of hypertonic saline into the forearm produced significantly higher pain scores in the dysmenorrheic women compared to the controls as assessed by peak VAS (group effect: $F[1, 19] = 8.0$,

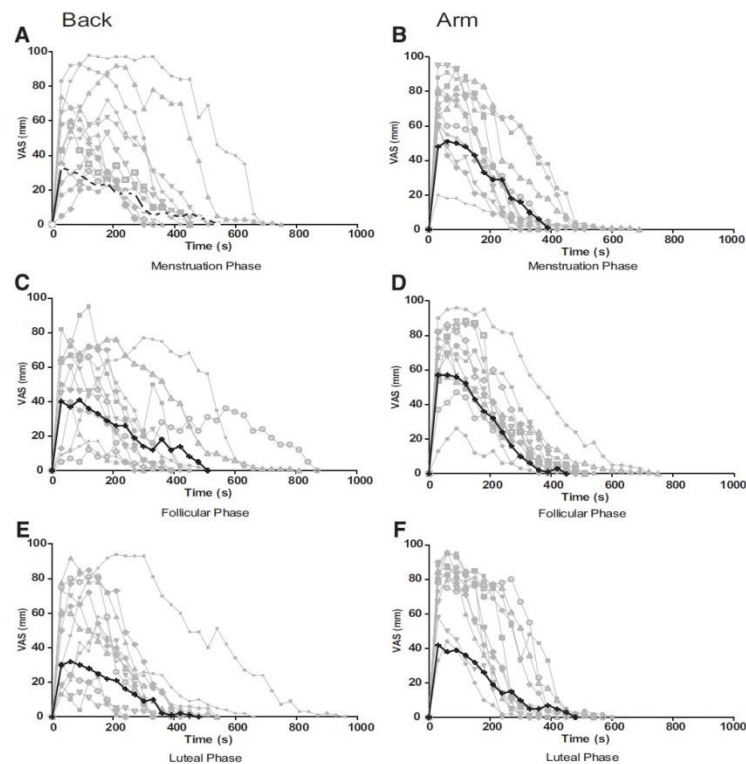


Figure 2. VAS ratings of pain intensity every 30 seconds from the time of an intramuscular injection of hypertonic saline ($t = 0$) into the lumbar erector spinae muscle (lower back, **A**, **C**, **E**) or into the extensor muscles of the forearm (**B**, **D**, **F**) during the menstruation (**A**, **B**), follicular (**C**, **D**), and luteal (**E**, **F**) phases of the menstrual cycle. The gray lines represent the individual data for each of the 12 women with primary dysmenorrhea, and the bold black line represents the mean VAS rating for the control group ($n = 9$); SD bars are omitted for clarity.

$P = .01$, total duration of muscle pain (group effect: $F[1, 19] = 8.0$, $P = .01$), and AUC (group effect: $F[1, 19] = 7.1$, $P = .02$) (Fig 4). There were no significant menstrual phase effects on peak VAS (phase effect: $F[2, 38] = .6$, $P = .6$), pain duration (phase effect: $F[2, 38] = 2.2$, $P = .1$), or AUC (phase effect: $F[2, 38] = .4$, $P = .7$). There were also no significant group-phase interaction effects for pain duration ($F[2, 38] = 2.2$, $P = .1$) or AUC ($F[2, 38] = 1.2$, $P = .3$). However, there was a borderline significant group-phase interaction effect for peak VAS ($F[2, 38] = 6.1$, $P = .05$). The dysmenorrheic women had a significantly higher peak VAS rating than controls in the menstruation and luteal phases but not the follicular phase (Fig 4). As shown in Fig 4, post hoc comparisons revealed that dysmenorrheic women had significantly more severe pain based on measures of peak VAS and pain duration (SNK: $P < .05$), with a nonsignificant trend for a greater AUC (SNK: $P < .1$) than controls in the menstruation phase. In the follicular phase, post hoc comparisons showed that dysmenorrheic women had significantly more severe pain based on measures of pain duration and AUC (SNK: $P < .05$) and tended to have a higher peak VAS (SNK: $P < .1$) than controls. In the luteal phase, dysmenorrheic women had significantly greater peak VAS and AUC measures (SNK: $P < .05$) with a

nonsignificant trend for a greater pain duration (SNK: $P < .1$).

Discussion

In the present study, experimental deep muscle pain was induced in otherwise healthy women with severe primary dysmenorrhea and in healthy matched women without dysmenorrhea. In both groups of women, menstrual cycle phase had no effect on their reports of pain intensity and duration. However, women with dysmenorrhea, compared to women without dysmenorrhea, had increased sensitivity to experimental muscle pain when they were experiencing menstrual pain as well as in the pain-free phases of the menstrual cycle. Muscles both within and outside the area of referred menstrual pain were hypersensitive to pain in women with dysmenorrhea. These data suggest that deep muscle tissue is hypersensitive to pain across the menstrual cycle in women with dysmenorrhea, possibly because of long-lasting changes in the central nervous system leading to central sensitization.

The present study demonstrates that women with primary dysmenorrhea have increased sensitivity to a

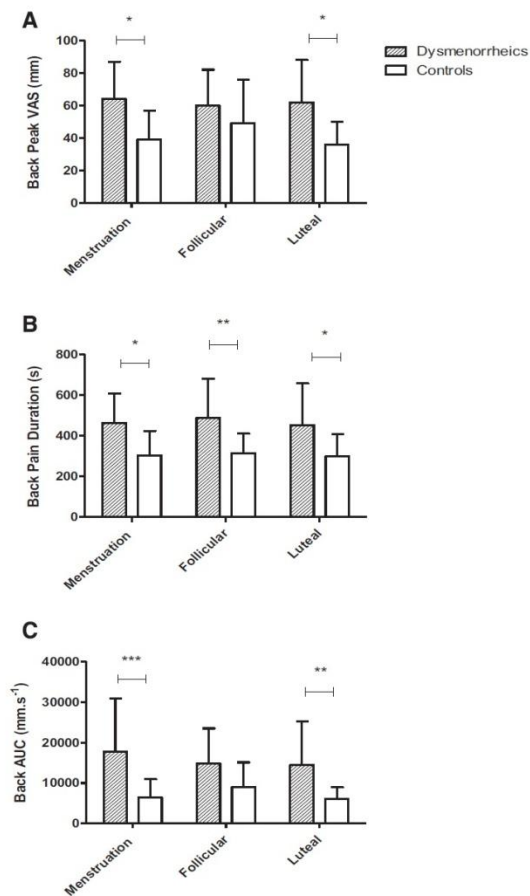


Figure 3. Pain response measurements from the VAS following an intramuscular injection of hypertonic saline into the lumbar erector spinae muscle (lower back). Peak VAS (mm) (A); total muscle pain duration (s) (B); and area under the curve (AUC, mm·s⁻¹) (C), are shown for 12 dysmenorrheic women and 9 control women in the menstruation, follicular, and luteal menstrual cycle phases. A 2-way repeated-measures ANOVA was used to assess for a main effect of group and phase, and SNK post hoc tests determined the origin of significant differences. *** $P < .001$, ** $P < .01$, * $P < .05$.

clinically relevant,^{6,29} clearly nociceptive deep muscle tissue pain induced by hypertonic saline injection. Studies that have investigated sensitivity to pain in women with dysmenorrhea using other nociceptive stimuli have produced conflicting results, with some studies reporting no differences in the perception of pain between dysmenorrheic and nondysmenorrheic women^{1,3,8,22,26,28} and others reporting either increased^{8,22,28} or decreased³³ sensitivity to experimental pain stimuli in women with dysmenorrhea compared to controls. Discrepancies between studies may exist, in part, because experimental pain modalities that target the skin and subcutaneous tissues rather than those that target deep muscle were used. Muscles are the tissues most likely to become hyperalgesic under recurrent pain conditions.^{22,23,71} In line with previous studies,^{22,74} we have shown that an increased

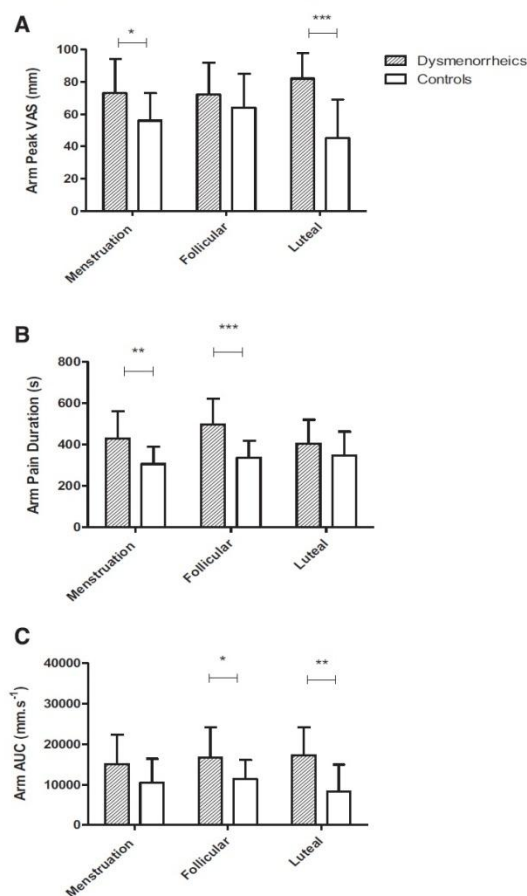


Figure 4. Pain response measurements from the VAS following an intramuscular injection of hypertonic saline into the extensor muscles of the forearm. Peak VAS (mm) (A), total muscle pain duration (s) (B), and area under the curve (AUC, mm·s⁻¹) (C) are shown for 12 dysmenorrheic women and 9 control women in the menstruation, follicular, and luteal menstrual cycle phases. A 2-way repeated-measures ANOVA was used to assess for a main effect of group and phase, and SNK post hoc tests determined the origin of significant differences. *** $P < .001$, ** $P < .01$, * $P < .05$.

pain response to deep muscle pain in women with dysmenorrhea is apparent both within and outside the area of referred menstrual pain. This finding suggests that women with dysmenorrhea may have altered pain processing throughout the central nervous system, which is more widespread than just those parts serving areas exposed to referred pain.

As part of our study, we investigated whether pain sensitivity varied as a function of menstrual cycle phase in women with dysmenorrhea compared to controls. We found no main effect of menstrual cycle phase or group-menstrual phase interaction effect despite the substantial measured differences in progesterone and/or estradiol concentrations between phases, suggesting that variation in reproductive hormones does not impact pain sensitivity in women with and without dysmenorrhea. Although our

sample size was small, these findings are in agreement with several other studies in both women with^{3,26,28,74} and without^{3,8,15,17,18,28,41,42,44,45,53,56,57,61,64,72,74} dysmenorrhea. Others, however, have reported that pain responses vary according to menstrual cycle phase in women with^{8,22,33} and without dysmenorrhea.^{8,17,22,25,26,28,33,34,36,39,43,54,56,57,59,62,66} However, as described in several reviews,^{19,58,60} most studies were confounded because they did not confirm menstrual cycle phase and/or the presence of ovulatory cycles based on hormone measurements. The precise roles of gonadal hormones in pain perception are not fully understood and the underlying mechanisms have yet to be elucidated.¹³ However, data from the current literature show that estrogen and progesterone can generate both antinociceptive and pronociceptive effects.^{15,47,51,62,70} The interaction, therefore, between gonadal hormones and pain perception is complex, and the net effect of ovarian hormones on pain perception may depend on the sum of their pronociceptive and antinociceptive effects.⁴⁹

In this study, the women with dysmenorrhea were screened to ensure that they experienced pain only during menstruation. To determine whether pain intensity and duration following induction of experimental pain was influenced by the existing background menstrual pain, we included the menstruation phase as one of the menstrual cycle phases during which we assessed experimental pain. Similar to other reports,^{21,74} we found that enhanced pain intensity and duration in women with dysmenorrhea was not limited only to the phase of menstruation itself but was present in the follicular and luteal phases of the menstrual cycle. The enhanced response to a painful stimulus both 1) at a site different from that of the referred clinical pain (arm) and 2) in the absence of background (menstrual) pain suggests long-lasting changes in pain processing possibly because of recurrent dysmenorrheic pain. Our results support the hypothesis that dysmenorrhea is a pain disorder that can persist throughout the entire menstrual cycle, and not merely during menstruation.^{21,74}

Our findings of hyperalgesia in women with dysmenorrhea support a growing body of literature suggesting the presence of central sensitization in dysmenorrheic women,^{68,69,74} particularly affecting muscle. Progressively more data are verifying the notion that structural and functional modifications within the central nervous system can be induced by the recurrent painful episodes experienced by women with dysmenorrhea^{68,69,74} and not only in chronic pain conditions characterized by persistent pain.^{7,9,14} It has been hypothesized previously that central reorganization in women with dysmenorrhea induces a combination of impaired pain inhibition and amplified pain facilitation.⁶⁸ Importantly, these morphologic brain changes and behavioral changes to noxious stimulation found in other studies are evident in pain-free phases of the menstrual cycle.^{8,22,74} Our results confirm that behavioral changes to noxious stimulation are apparent in pain-free phases of the menstrual cycle in women with dysmenorrhea.

Although primary dysmenorrhea is not typically regarded as a chronic pelvic pain condition,² it is a frequent comorbid symptom in women with chronic pelvic pain.⁷⁷ For example, a robust 10-year follow-up study concluded that women with irritable bowel syndrome are more likely to experience dysmenorrhea compared to women without irritable bowel syndrome.⁵² In addition, dysmenorrheic women have been found to display many of the features associated with chronic pelvic pain, including suppression of the hypothalamic–pituitary–adrenal axis, a reduction in quality of life, and altered central processing of nociceptive inputs.^{4,74} The above findings raise the question of whether dysmenorrhea underlies or predisposes women to other chronic painful conditions.

Also of importance is that the observed abnormal volume changes in the gray matter of women with primary dysmenorrhea⁶⁸ are similar to those found in other chronic pain states.^{7,9} Longitudinal studies suggest that the central changes in chronic pain states are dynamic and reversible after removal of the nociceptive source.^{31,67} Extending the significance of these data to women with dysmenorrhea, effective treatment of repetitive dysmenorrheic pain, and thereby decreasing the input of repeated noxious stimuli to the central nervous system, may reverse or prevent the central changes. Future studies should investigate whether central and behavioral changes are still present after effective treatment of dysmenorrhea.

Our results should be interpreted in context of the limitations of the study. The sample was small such that there was low statistical power for some of the post hoc analyses. However, findings were robust for the ANOVA models and the study has numerous methodologic strengths that reinforce confidence in the results. Unlike many previous studies, we confirmed menstrual cycle phase with the use of ovulation kits and hormonal assays of progesterone and estrogen. Our within-subject design also helps to control for the biological differences (and any other variables) that would influence pain perception, thereby making our results of pain assessment across the menstrual cycle meaningful. Importantly, we also evaluated mood in our subjects, given that mood alters pain perception.^{65,73} As the women with dysmenorrhea had significantly poorer moods than the women without dysmenorrhea during the menstruation phase experimental session, it is possible that mood played a role in the enhanced perception to the noxious stimuli during that session. However, a poor mood cannot account for the difference in pain perception of the dysmenorrheic women compared to controls in the remaining phases of the menstrual cycle.

In conclusion, we have confirmed that primary dysmenorrhea is associated with increased pain sensitization across the menstrual cycle in areas of referred pain and remote sites compared to women without dysmenorrhea. Without a longitudinal study, it is not possible to identify whether the increased sensitivity to muscle pain in women with dysmenorrhea is the cause,

or the effect, of the recurrent menstrual pain. Either way, limiting the cyclic noxious input to the central nervous system in women with severe dysmenorrhea, by effective

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analgesic treatment, could reduce the chances of developing hyperalgesia and possibly other chronic pain conditions.

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CHAPTER TWO

Women with Primary Dysmenorrhoea are Hypersensitive to Experimentally-Induced Forearm Ischaemia during Painful Menstruation and during the Pain-Free Follicular Phase

ABSTRACT

Monthly primary dysmenorrhoeic pain, or painful menstruation, has been hypothesised to lead to increased sensitivity to painful stimuli, particularly in deep-tissue. We investigated whether women with primary dysmenorrhoea, compared to women without dysmenorrhoea, have increased sensitivity to experimentally-induced deep-tissue muscle ischaemia in a body area distant from that of referred menstrual pain. The sub-maximal effort tourniquet test was used to induce forearm ischaemia in 11 women with severe primary dysmenorrhoea and in 9 women without dysmenorrhoea (controls) both during menstruation and in the follicular phase of the menstrual cycle. Von Frey Hair assessments confirmed the presence of experimental ischaemia. Women rated the intensity of menstrual and ischaemic pain on a 100 mm visual analogue scale. Women with dysmenorrhoea (mean $\pm$ SD: 68 $\pm$ 20 mm) reported significantly greater menstrual pain compared to controls (mean $\pm$ SD: 3 $\pm$ 6 mm; $P = 0.0001$) during the menstruation phase. They also rated their forearm ischaemic pain as significantly greater than the controls during the menstruation (dysmenorrhoeics vs. controls mean $\pm$ SD: 58 $\pm$ 19 mm vs. 31 $\pm$ 21 mm, $P < 0.01$) and follicular (dysmenorrhoeics vs. controls mean $\pm$ SD: 60 $\pm$ 18 mm vs. 40 $\pm$ 14 mm, $P < 0.01$) phases of the menstrual cycle. These data show that compared to women without dysmenorrhoea, women who experience severe recurrent primary dysmenorrhoea have deep-tissue hyperalgesia to ischaemic pain in muscles outside of the referred area of menstrual pain both during the painful menstruation phase and pain-free follicular phase. These findings suggest the presence of long-lasting changes in pain sensitivity, or central sensitisation, particularly in muscle tissue, in women with primary dysmenorrhoea.

INTRODUCTION

Primary dysmenorrhoea, defined as painful, spasmodic cramping in the lower abdomen, just before and/or during menstruation, in the absence of any discernible macroscopic pelvic pathology⁹, is the most common gynaecological disorder in women of a reproductive age^{6,16}. It has been hypothesised that the experience of this recurrent pain leads women with primary dysmenorrhoea to be hypersensitive to other pain^{18,22}, although findings have been mixed, with some studies supporting this hypothesis^{4,10-13,20} and others showing no difference in sensitivity to experimental pain in women with primary dysmenorrhoea compared to non-sufferers^{1,2}.

We previously showed that women with primary dysmenorrhoea are hypersensitive to deep muscle pain induced by injection of hypertonic saline¹⁴ (Chapter 2a) compared to controls both within referred and non-referred areas of menstrual pain, during the painful menstruation phase and during pain-free phases of the menstrual cycle. To follow up on these findings, we aimed to determine whether women with primary dysmenorrhoea are also hypersensitive to another deep-muscle pain, induced by ischaemia.

Experimental ischaemia is considered to be a more natural “endogenous” muscle pain-producing technique, which differs from “exogenous” muscle-pain producing techniques such as injection of hypertonic saline and electrical stimulation of muscle afferents¹⁷. Experimentally-induced ischaemia produces a deep, aching pain, similar to that experienced by patients with many clinical pain syndromes. It is relevant to the study of dysmenorrhoea given that the menstrual pain is ischaemic in origin⁹. Only two previous studies investigated pain responses to

experimental muscle ischaemia and both found no difference in thresholds or tolerance between women with dysmenorrhoea and control women across three phases of the menstrual cycle ^{1,2}, although women with dysmenorrhoea rated the ischaemic pain as more severe ². The interpretation of these two studies is complicated, however, by the fact that dysmenorrhoeic women were divided into subgroups based on whether their menstrual pain occurred before menstruation, during menstruation, or both.

The aims of this study were to determine whether women with severe primary dysmenorrhoea have increased sensitivity to muscle ischaemia in a body area distant from that of referred menstrual pain, both when they are experiencing pain (during menstruation) and in a pain-free follicular phase of the menstrual cycle, compared to controls.

METHODS

Women who participated in the study described in Chapter 2a were invited to participate in this additional experiment during another menstrual cycle. Procedures were approved by the University of the Witwatersrand's Committee for Research on Human Subjects under the same protocol presented in Chapter 2a (Clearance no. M080627). Eleven women with a history of primary dysmenorrhoea and nine women without a history of dysmenorrhoea completed the experiment. The group of women with dysmenorrhoea included 4 black, 1 mixed-race, 1 Indian and 5 white women. While the control group included 5 black women and 4 white women. Subject characteristics are presented in Table 1.

Table 1. Characteristics of the women who participated in the study.

	Women with dysmenorrhoea (n = 11)	Control women (n = 9)	P value
Age (years)	21 ± 3	22 ± 2	0.36
Weight (kg)	60.5 ± 12.9	60.7 ± 12.7	0.97
Height (m)	1.6 ± 0.1	1.61 ± 0.04	0.79
Body Mass Index (kg/m ²)	22.9 ± 3.9	23.2 ± 4.0	0.88
Age of onset of menses (years)	13 ± 2	14 ± 1	0.21
Age of onset of dysmenorrhoea (years)	14 ± 2	-	N/A
Usual menstrual cycle length (days)	28 ± 0	28 ± 1	0.18
Usual menstruation phase length (days)	5 ± 1	4 ± 1	0.23
Average menstrual pain intensity (for previous 6 months; VAS, mm)	68 ± 20	2 ± 6	0.0001*

Data are expressed as mean ± SD

**** Significant difference between the dysmenorrhoeic and control groups (Student's unpaired 2-tail t-test)***

Experimental phase

Women visited the laboratory on two separate occasions between 12:00 and 14:00, once during the menstruation phase (days 1-2; where day 1 refers to the first day of menstruation) and once during the late-follicular phase (days 11-13); the order of which was randomised.

In both groups of women, forearm ischaemia was induced to simulate uterine ischaemia, as experienced during menstruation by women with primary dysmenorrhoea, but in muscles outside the area of referred menstrual pain. Forearm ischaemia was induced in a randomly selected arm by means of the sub-maximal effort tourniquet test, a standard procedure involving the occlusion of blood flow in the arm with a tourniquet cuff (200 mmHg) positioned above the elbow¹⁵. After inflating the cuff, in order to promote forearm ischaemia, the women performed 20 hand-grip exercises, at 30% of their maximal hand-grip strength, using a hand-grip dynamometer. The duration of each squeeze was 2 seconds with an inter-squeeze interval of 2 seconds. Once the 20 hand-grip exercises had been executed, the cuff remained inflated for 10 minutes. After the 10 minutes of ischaemia, with the cuff still inflated, the women were asked to rate the intensity of the ischaemic pain using a 100 mm VAS anchored at “no pain at all” to “the worst pain ever”.

To ensure that forearm ischaemia was indeed achieved after performing the sub-maximal effort tourniquet test, Von Frey hairs (Semmes-Weinstein Monofilaments), carrier-mounted 40 mm-long nylon monofilaments of varying diameter (0.064 to 1.143mm) were used (Touch-TestTM Sensory Evaluator, North Coast Medical Inc, Morgan Hill, CA, 2002)²¹ to assess mechanical sensation of the skin. While the women were blindfolded, the Von Frey hairs, starting from the

finest filament, were applied perpendicularly (at 90 degrees) to the anterior skin surface of the distal phalanx of the index finger until the Von Frey hair buckled in the middle. This was done both before the cuff was inflated (pre-ischaemia) and after the 10 minutes of cuff inflation (during ischaemia). The filament with the smallest diameter that was felt by each woman was recorded.

Assessment of menstrual pain

During the menstruation phase, at the start of each experimental session, both groups of women assessed the intensity of their menstrual pain on a 100mm VAS anchored from “no pain at all” to “the worst pain I have ever felt”. None of the women took medication for menstrual pain alleviation on the days of the experiment.

Statistical Analyses

All data were analysed using STATISTICA (version 5, 1996). A two-tailed probability of $P \leq 0.05$ was considered to be statistically significant. All VAS measurements (in mm), used to describe the intensity of dysmenorrhoeic and ischaemic pain, were normalised before statistical analyses using the arcsine transformation. However, all text and graphs report the VAS data as back transformed values (in mm). The standard deviations of back transformed data are asymmetric. However, only the standard deviation values above the mean are presented. All values are expressed as mean $\pm$ standard deviation (SD).

Student's unpaired *t*-tests were used to compare demographic variables (age, anthropometric variables and menstrual history), as well as menstrual pain intensity (VAS, mm), between the two groups of women. All VAS measurements were analysed according to group (dysmenorrhoeics and controls) and menstrual cycle phase (menstruation and follicular) using two-way repeated-measures ANOVAs. Where appropriate, the Student-Newman-Keuls post-hoc test was used to assess the origin of any significant differences detected by the ANOVA models.

Similarly, Von Frey measurements were analysed using a two-way-repeated-measures ANOVA according to group (dysmenorrhoeics and controls) and muscle state within each menstrual cycle phase (menstruation pre-ischaemic, menstruation ischaemic and follicular pre-ischaemic, follicular ischaemic). Where appropriate, the Student-Newman-Keuls post-hoc test was used to assess the origin of any significant differences detected by the ANOVA models.

RESULTS

Menstrual pain

An unpaired *t*-test comparing menstrual pain intensity (VAS) in the two groups of women confirmed that women with dysmenorrhoea were experiencing significantly more menstrual pain (mean $\pm$ SD: 68 $\pm$ 20 mm) compared to the control women (mean $\pm$ SD: 3 $\pm$ 6 mm; $t(18) = 9.5$; $P = 0.0001$) at the time of the experiment. Eight of the eleven women with dysmenorrhoea were experiencing severe (> 60 mm on the VAS)⁷ menstrual pain at the start of the experiment.

Confirming Forearm Ischaemia with Von Frey Hairs

Von Frey Hair assessments on the index finger of the arm being tested before and after the sub-maximal tourniquet test used to induce ischaemia confirmed that, in both phases of the menstrual cycle (menstruation and follicular), both groups of women lost a significant amount of tactile sensation because of the ischaemia (ischaemia status (pre- vs ischaemia): $F(3,54) = 24.89$; $P < 0.0001$). Table 2 shows the results of the Newman-Keuls Post hoc analyses.

Table 2. Von Frey Hair measurements and P-values obtained by the Newman-Keuls Post hoc analyses following a two-way RM-ANOVA to confirm a state of ischaemia.

	Menstruation Phase			Follicular Phase		
	<i>Pre-Ischaemia</i>	<i>Ischaemia</i>	<i>P-value</i> ‡	<i>Pre-Ischaemia</i>	<i>Ischaemia</i>	<i>P-value</i> ‡
Dysmenorrhoeics	2.66	3.13	0.002*	2.66	3.10	0.002*
Controls	2.70	3.31	0.0002*	2.93	3.34	0.006*

‡ *P-values obtained by two-way-ANOVAs followed by Newman-Keuls Post hoc analyses*

* *P < 0.05 comparing pre-ischaemia and ischaemia*

Ischaemic pain

Women with dysmenorrhoea rated the experimental forearm ischaemic pain as significantly greater (VAS mean $\pm$ SD: menstruation phase 58 ± 19 mm, follicular phase: 60 ± 18 mm) than the controls (VAS mean $\pm$ SD: menstruation phase: 31 ± 21 mm, follicular phase: 40 ± 14 mm) in both phases of the menstrual cycle (Figure 1). There was a significant group effect ($F(1,18) = 12.27$; $P = 0.003$), but phase ($F(1,18) = 1.59$; $P = 0.2$) and group-phase interaction effects ($F(1,18) = 0.44$; $P = 0.5$) were not significant.

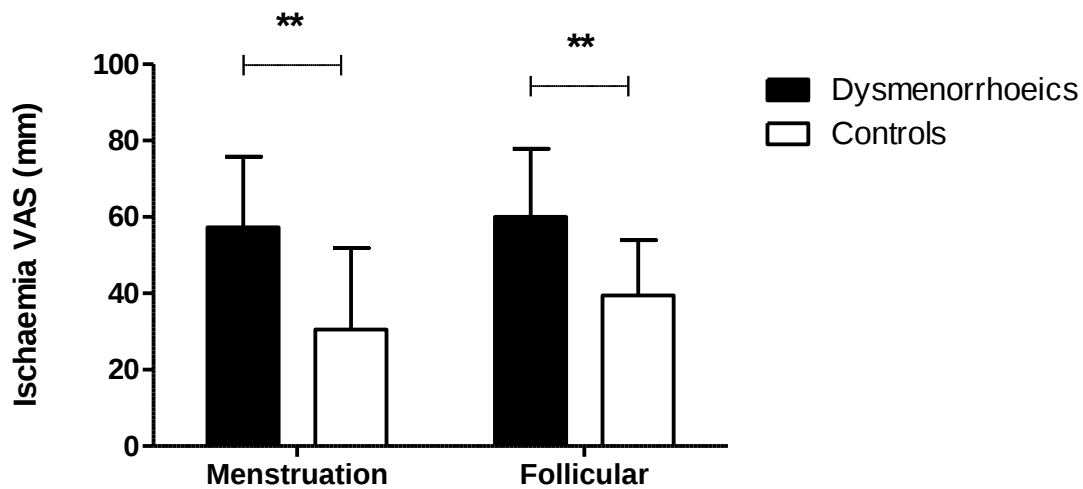


Figure 1. Ischaemic pain intensity from the Visual Analogue Scale (VAS) following the sub-maximal effort tourniquet test¹⁵ shown for eleven dysmenorrhoeic women and nine control women in the menstruation and follicular phases of the menstrual cycle. A two-way repeated-measures analysis of variance was used to assess for a main effect of group and phase, and Newman-Keuls posthoc tests determined the origin of significant differences.

**** $P < 0.01$**

DISCUSSION

The main objective of this study was to compare the ischaemic pain sensitivity of women with primary dysmenorrhoea to that of women without dysmenorrhoea. The results of this study demonstrate that women with a history of severe primary dysmenorrhoea are hypersensitive to tourniquet-induced forearm ischaemia compared to women without dysmenorrhoea, both during menstruation (when experiencing menstrual pain) and during the pain-free follicular phase.

To my knowledge, this study is the first to show that women with primary dysmenorrhoea are more sensitive to experimental muscle ischaemia compared to non-dysmenorrhoeic control women. These findings extend those presented in Chapter 2a¹⁴ by showing that women with primary dysmenorrhoea have increased sensitivity to exogenous (hypertonic saline) and endogenous (ischaemia) experimental muscle pain, compared to women without dysmenorrhoea. Further, these two studies show that the hypersensitivity in women with dysmenorrhoea is evident when they are experiencing physiological pain during menstruation as well as during pain-free phases of the menstrual cycle. These findings, together with evidence that women with dysmenorrhoea are hypersensitive to thermal pain across the menstrual cycle²⁰, collectively strengthen the growing body of literature suggesting the presence of long-lasting changes in pain sensitivity, or central sensitisation, particularly in muscle tissues, in women who experience monthly dysmenorrhoea^{4,10,12}. Furthermore, this study substantiates previous reports^{4,10,14,20} that hyperalgesia in women with dysmenorrhoea is widespread, as it extends to areas of non-referred menstrual pain.

Progressively more data are verifying the notion that structural and functional modifications within the central nervous system can be induced by recurrent painful episodes, as experienced by women with dysmenorrhoea ¹⁸⁻²⁰, and not only in chronic pain conditions characterised by persistent pain ^{3,5,8}. The recently described morphologic and functional brain changes in women with dysmenorrhoea ^{18,19} have been hypothesised to induce a combination of impaired pain inhibition and amplified pain facilitation ¹⁸. The findings of both my studies described in this Chapter (Chapter 2a and 2b) support this hypothesis by providing further evidence of changes in behavioural responses to endogenous (ischaemia) and exogenous (hypertonic saline) noxious stimulation to muscles that extend to pain-free phases of the menstrual cycle, and to areas outside of referred menstrual pain in women with primary dysmenorrhoea. My findings therefore support the presence of long-lasting changes in pain sensitivity, or central sensitisation, particularly in deep-muscle tissue, in women with primary dysmenorrhoea.

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CHAPTER THREE

Paper 2:

***Reduced Quality of Life when Experiencing Menstrual Pain in
Women with Primary Dysmenorrhoea***

From: torbjorn.backstrom@obgyn.umu.se [torbjorn.backstrom@obgyn.umu.se]

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To: susana.benedet@gu.se

Cc: Stella Iacovides; Ingrid Avidon; Alison Bentley; Fiona.Baker@sri.com

Subject: Acta Obstetricia et Gynecologica Scandinavica (AOGS) - Decision on Manuscript ID AOGS-13-0360.R1

13-Oct-2013

Dear Dr. Stella Iacovides:

Ref: AOGS-13-0360.R1 - Reduced Quality of Life When Experiencing Menstrual Pain in Women with Primary Dysmenorrhea

We thank you and your co-authors for submitting your revised manuscript to Acta Obstetricia et Gynecologica Scandinavica (AOGS). Your detailed replies were appreciated. We have now considered it again at Editorial Board level. We are pleased to let you know that the manuscript has been accepted for publication in Acta Obstetricia et Gynecologica Scandinavica (AOGS).

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Thank you for your contribution to Acta Obstetricia et Gynecologica Scandinavica (AOGS) and we look forward to receiving further submissions from you.

Sincerely,

Professor Torbjörn Bäckström MD, PhD

Associate Editor

Acta Obstetricia et Gynecologica Scandinavica (AOGS)

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Reduced Quality of Life When Experiencing Menstrual Pain in Women with Primary Dysmenorrhea

Running headline: Menstrual pain reduces quality of life during menstruation

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ABSTRACT

Primary dysmenorrhea is the most common gynecological condition among women of reproductive age. Although dysmenorrhea has been reported to affect the ability of women to carry out daily activities, the impact of primary dysmenorrheic pain specifically on quality of life (QoL), has yet to be elucidated. We investigated whether QoL varies between women with, and without, severe primary dysmenorrhea, and whether QoL is impaired only during menstruation or also during pain-free phases of the menstrual cycle. Twelve women with severe primary dysmenorrhea and nine control women completed the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF) during menstruation and during the late-follicular phase. Women with dysmenorrhea had a significant reduction in Q-LES-Q-SF scores (mean $\pm$ SD: 54% $\pm$ 18, percentage of the total maximum possible score) when they were experiencing pain severe menstrual pain compared to their own pain-free follicular phase (80% $\pm$ 14, $P < 0.0001$) and compared to controls during menstruation (81% $\pm$ 10, $P < 0.0001$). They also rated their overall life satisfaction and contentment as poorer during menstruation. Severe menstrual pain associated with primary dysmenorrhea, therefore, impacts health-related of quality of life.

KEYWORDS

Quality of life, dysmenorrhea, pain, menstruation, menstrual phase, women.

ABBREVIATIONS

ANOVA: analysis of variance; PMS: premenstrual syndrome; Q-LES-Q-SF: quality of life enjoyment and satisfaction-short form questionnaire; QoL: quality of life; SD: standard deviation; VAS: visual analogue scale.

KEY MESSAGE

By excluding women with secondary dysmenorrhea and accounting for menstrual cycle phase and pain intensity, we conclude that women with severe primary dysmenorrhea have a significant reduction in quality of life during menstruation compared to their own pain-free follicular phase and compared to controls during menstruation.

INTRODUCTION

Health-related quality of life (QoL) represents how an individual perceives the impact of a health condition on daily living and is one of the most significant patient-reported outcome measures (1, 2). In pain research particularly, QoL measures have been reported to be more responsive to changes in the clinical condition than pain measures themselves (1). Pain is one of the largest contributors to poor QoL (1). Many chronic pain conditions, such as neuropathic pain (3), are associated with reduced QoL. Primary dysmenorrhea is a recurrent pain condition, in which women experience acute episodes of painful cramping linked to menstruation, in the absence of pelvic pathology (4).

Irrespective of nationality and age, primary dysmenorrhea is the most common gynecological condition among menstruating women (4). Dysmenorrheic pain can be considerably disabling, and is associated with a restriction of physical and daily activities (5). Yet, few studies have evaluated QoL as a specific construct in women with primary dysmenorrhea. Studies have reported lower health-related QoL in women with dysmenorrhea (6-9); however, they did not distinguish between primary and secondary dysmenorrhea (pain originating from a number of identifiable pathological conditions, such as endometriosis and pelvic inflammatory disease (10), and only one considered the intensity of dysmenorrheic pain (6). Moreover, these studies did not take menstrual cycle phase into account (6-9), and therefore have not considered whether QoL in women with dysmenorrhea is persistently lower compared to women without dysmenorrhea, or whether the decrease in QoL is specifically linked to menstrual pain. QoL can continue to be impacted even in the absence of overt symptoms. For example, women with severe premenstrual

syndrome, another condition linked to a specific menstrual phase, report poorer QoL not only in the premenstrual phase but also in the low-symptom follicular phase, compared to controls (11).

Also, the impact of pain on QoL depends on the frequency of painful episodes; with impairment of QoL being less pronounced with monthly, versus weekly, painful episodes (12, 13). Given that women with primary dysmenorrhea experience pain monthly, their QoL may not be impacted to the same extent as it is in chronic pain conditions. Indeed in studies of patients with a wide range of illnesses, a longer duration and more chronic nature of pain was associated with a poorer QoL (1). Further, given that many women consider dysmenorrhea to be a normal part of the menstrual cycle, rather than a disorder (14), it is plausible that they have, in fact, learned to live or cope with its effects, and thus lessen the disorder's impact on QoL.

We used the validated Short Form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF) (15) to determine whether QoL differs between women with primary dysmenorrhea and women without dysmenorrhea (controls) when they are experiencing menstrual pain as well as in a pain-free phase of the menstrual cycle.

MATERIALS AND METHODS

Methodology of subject recruitment on a different group of women is described elsewhere (16). Briefly, volunteers were interviewed, completed questionnaires, and underwent a month-long screening period to ensure that they were generally healthy, had regular ovulatory menstrual cycles (self-test ovulation kits), normal psychological status, no severe PMS, no indications of secondary causes for dysmenorrhea, and no chronic illness. Women were then allocated to either the “dysmenorrheic” or “non-dysmenorrheic/control” group. To be included in the dysmenorrheic group, the women were required to have a history of dysmenorrhea, starting shortly after menarche, which distinguishes primary from secondary dysmenorrhea (4), and rate menstrual pain as “severe”; defined as a score ≥ 60 mm on a 100-mm visual analogue scale (VAS), based on the work of others showing that > 54 mm defines severe pain (17). Women were included in the control group if they rated their menstrual pain as less than 30-mm on the VAS (17).

Twelve women with a history of primary dysmenorrhea and nine controls met the inclusion criteria, and gave written informed consent to participate in the study. Ethical clearance was obtained from the University of the Witwatersrand’s Committee for Research on Human Subjects, which adheres to the principles of the Declaration of Helsinki (Clearance no. M080627).

Women completed the short form of the Quality of Life Enjoyment and Satisfaction- Short Form (Q-LES-Q-SF) questionnaire once during the menstruation phase (when experiencing pain, day 1 of the menstrual cycle) and once during the late-follicular phase (when pain-free, days 10-12);

the order of which was randomized. The Q-LES-Q-SF is a validated, self-reported evaluation of the degree to which enjoyment and satisfaction are derived from various areas of life. The Q-LES-Q-SF was derived from the general activities scale of the original 93-item questionnaire (15), and has been found to offer high internal consistency, reproducibility, reliability, and validity in patients with other painful conditions. It has also been successfully used to distinguish changes in QoL across the monthly menstrual cycle in women with severe premenstrual syndrome (18). The Q-LES-Q-SF consists of items that evaluate overall enjoyment and satisfaction regarding: physical health, mood, work, household and leisure activities, family and social relationships, ability to function in daily life, sexual drive, economic status, living/housing situation, ability to get around physically, ability to do work or hobbies, and overall sense of being. Responses were scored on a 5-point scale (from ‘very poor’ to ‘very good’), where higher scores indicate better enjoyment and satisfaction with life (possible range of raw total score: 14–70) (19). Scores were added and presented as a percentage of the total maximum possible score. A percentage of total score of ≥ 70 represents normal QoL in a community sample (18). An additional item (item 16) measured overall life satisfaction and contentment during the past week, on a 5-point scale.

During the menstruation phase, the women rated the intensity of their current menstrual pain on a 100mm VAS anchored from “No Pain” to “The worst pain I have ever experienced”. None of the women used pain-relieving medication on the day of assessment.

A two-way repeated-measures analysis of variance (ANOVA) was used to assess any differences in Q-LES-Q-SF scores (percentage of maximum possible scores) between the two groups of

women during the menstruation and follicular menstrual cycle phases. Where appropriate, the Student-Newman-Keuls post-hoc test was used to assess the origin of any significant differences detected by the ANOVA models. Scores on item 16 were compared between groups during menstruation using a Mann-Whitney test and between the menstruation and follicular phases for the dysmenorrheic group using a Wilcoxon matched-pairs signed-ranks test. Bonferroni's correction was applied. Student's unpaired *t*-tests were used to compare the demographic variables and menstrual pain intensity (VAS, mm) between the two groups of women. A Pearson's correlation was used to determine whether there was an association between Q-LES-Q-SF scores (%) and dysmenorrheic pain intensity (VAS, mm).

RESULTS

Unpaired *t*-tests confirmed that the two groups of women were well-matched for age, anthropometric variables and menstrual history (Table 1). Women with dysmenorrhea had experienced significantly more severe menstrual pain during the past 6 months compared to controls.

Table 1. Characteristics of the women who participated in the study.

	Women with dysmenorrhea (n = 12)	Control women (n = 9)	P value
Age (years)	21 ± 2	22 ± 2	0.33
Weight (kg)	59.2 ± 13.0	60.7 ± 12.7	0.81
Height (m)	1.61 ± 0.07	1.61 ± 0.04	0.94
Body Mass Index (kg/m ²)	22.7 ± 3.8	23.2 ± 4.0	0.77
Age of onset of menses (years)	13 ± 2	14 ± 1	0.21
Age of onset of dysmenorrhea (years)	14 ± 2	-	N/A
Usual menstrual cycle length (days)	28 ± 0	28 ± 1	0.18
Usual menstruation phase length (days)	5 ± 1	4 ± 1	0.23
Average menstrual pain intensity (for previous 6 months; VAS, mm)	82 ± 12	4 ± 7	<0.0001*

Data are expressed as mean ± SD. VAS, visual analogue scale

Abbreviation: N/A, not applicable

** Significant difference between the dysmenorrheic and control groups (Student's unpaired 2-tail t-test)*

Women with dysmenorrhea experienced significantly more severe menstrual pain at the time of completing the questionnaires during the menstruation phase, compared to controls [VAS scores (mean $\pm$ SD): 68 $\pm$ 20mm versus 3 $\pm$ 6mm); Student's unpaired 2-tailed *t*-test: *t*(19)= 9.53; *P*= 0.0001].

There were significant group [F(1,19)= 5.58; *P*= 0.03], phase [F(1, 19)= 14.70; *P*= 0.001] and group-phase interaction [F(1, 19)= 80.43; *P*< 0.0001] effects for Q-LES-Q-SF scores. Women with dysmenorrhea reported a poorer QoL in the menstruation phase (mean $\pm$ SD: 54% $\pm$ 18) compared to controls (81% $\pm$ 10) [*P*< 0.0001] and compared to their own pain-free follicular phase (80% $\pm$ 14) [*P*< 0.0001] (Figure 1). Women with dysmenorrhea had lower ratings of overall life satisfaction and contentment (item 16) than controls during menstruation (Mann-Whitney *U* = 12.5, *P* = 0.004), which were also lower than their own follicular phase ratings (Wilcoxin: *P* = 0.008). Individual items of the Q-LES-Q-SF are presented in Table 2. While not statistically analyzed, it appears that women with dysmenorrhea while experiencing menstrual pain had lower QoL scores in all domains, with the exceptions of economic status and living/housing situation.

Percentage Q-LES-Q-SF scores and dysmenorrheic pain intensity were not correlated (r^2 = 0.0087, *P*= 0.77).

Table 2. Quality of Life Enjoyment and Satisfaction Questionnaire-Short form scores from the women with dysmenorrhea and the control women during the menstruation and follicular phases of the menstrual cycle

		Women with Dysmenorrhea (n=12)		Controls (n= 9)	
		Menstruation	Follicular	Menstruation	Follicular
1	Physical Health	3 (2,4)	4 (4,4)	4 (4,5)	4 (4,4)
2	Mood	2 (2,2)	4 (3,4)	4 (4,4)	4 (4,4)
3	Work	2 (2,3)	4 (3,4)	4 (4,4)	4 (3,4)
4	Household activities	2 (2,3)	4 (3,4)	4 (4,4)	4 (3,4)
5	Social relationships	3 (2,4)	4 (3,5)	4 (3,4)	4 (4,4)
6	Family relationships	3 (3,4)	4 (3,4)	4 (4,5)	4 (4,4)
7	Leisure time activities	2 (2,3)	4 (3,5)	4 (3,4)	3 (3,4)
8	Ability to function in daily life	3 (2,3)	4 (4,5)	4 (4,5)	4 (3,5)
9	Sexual drive, interest and/or performance	2 (2,3)	4 (2,5)	4 (3,4)	4 (3,4)
10	Economic status	3 (3,4)	3 (3,3)	3 (3,4)	4 (3,4)
11	Living/housing situation	4 (4,4)	4 (4,4)	4 (3,4)	4 (4,4)
12	Ability to get around physically without feeling dizzy or unsteady or falling	3 (3,4)	5 (4,5)	4 (4,5)	4 (4,5)
13	Vision in terms of ability to do work or hobbies	3 (3,4)	5 (4,5)	4 (4,4)	4 (4,4)
14	Overall sense of well being	3 (2,3)	4 (4,5)	4 (4,4)	4 (3,5)
16	Overall life satisfaction and contentment during the past week	3 (3,3)	4 (3,4)	4 (4,4)	4 (3,4)
Raw total score		39 (36,45)	55 (50,60)	55 (54,58)	53 (50,56)

Data expressed as median (1st quartile, 3rd quartile)

***Item 15** (assessment of medication), was not included in any analyses of this study, as all women were not taking any chronic medication, and were asked to refrain from using any medication; including medication to relieve their menstrual pain.

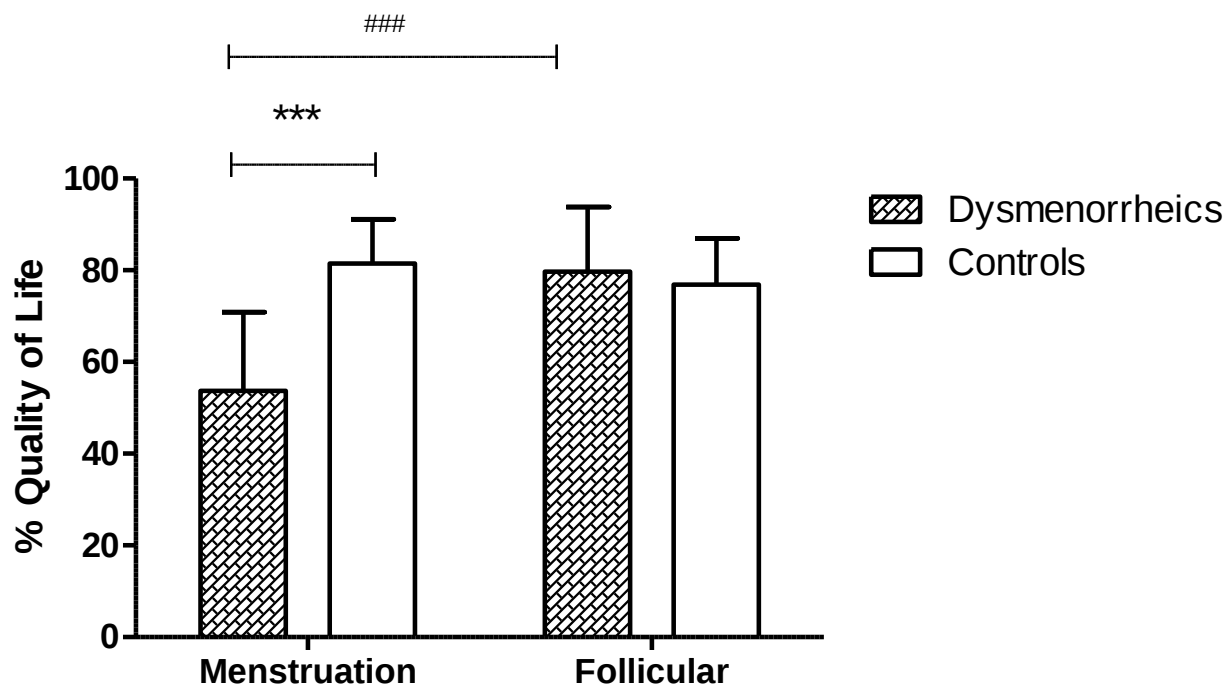


Figure 1. Quality of Life, expressed as a percentage (mean and SD), from the short form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF)[15] as rated by women with (n = 12) and women without (n = 9) primary dysmenorrhea during the menstruation and follicular menstrual cycle phases.

*** P < 0.0001 between women with and without dysmenorrhea during the menstruation phase.

P < 0.0001 between the menstruation and follicular phase in women with dysmenorrhea.

DISCUSSION

Severe dysmenorrheic pain is associated with a reduced QoL in women with dysmenorrhea, compared to their own pain-free follicular phase and compared to controls. Therefore, each month dysmenorrheic pain, negatively impacts QoL, specifically during menstruation.

Our results support those of previous cross-sectional studies showing reduced health-related QoL in women with dysmenorrhea (6-9). Previous studies, however, did not consider the menstrual cycle phase in which the questionnaire was completed (6-8), did not distinguish between primary and secondary dysmenorrheic pain (6-9), and some included women with other conditions including depression (7) or intermenstrual pelvic pain (9), which likely influenced QoL independent of dysmenorrheic pain. These studies also did not evaluate whether women had used pain-relieving medications for their dysmenorrhea at the time of assessment. Our results extend these data to show that untreated primary dysmenorrheic pain is associated with a reduced QoL only when pain is present; in the absence of menstrual pain, QoL in women with dysmenorrhea is similar to that of women without dysmenorrhea and a community sample (18).

Although the reduction in QoL was clearly linked to the presence of dysmenorrheic pain, pain severity and QoL were not correlated in the women with dysmenorrhea. It is likely that this result was due to our limited sample size and because we only included women with severe primary dysmenorrhea. A previous study of larger sample of women with a range of menstrual pain severity, found a significant decrease in most domains of QoL with increasing severity of dysmenorrhea (6).

We found a substantial reduction (26%) in overall QoL and an apparent impairment across almost all domains of QoL in women with dysmenorrhea during menstruation. Even though it is a familiar recurring pain with a predictable onset, primary dysmenorrhea, therefore, still impacts QoL. Patients with other chronic or cyclical painful conditions including neuropathic pain (3) and secondary dysmenorrhea (20) also have a poorer QoL, likely linked to their pain. Pain management is associated with a significant improvement in QoL (3). It is likely therefore, that successful management of dysmenorrheic pain would also improve QoL. Our findings suggest that measurement of QoL would be a useful indicator of the effectiveness of different treatments of dysmenorrhea.

A limitation of our study is the small sample size. However, the sample was well-characterized and adequate to detect a reduced QoL in women with primary dysmenorrhea, compared to controls, during menstruation. Our study had several methodological strengths. We assessed QoL in two groups of women (controls and dysmenorrheics), who completed comprehensive questionnaires and were screened to ensure that they did not have any medical or psychological disorders, including PMS. Given that PMS is often linked with dysmenorrhea, and that PMS is associated with a reduced QoL (11), it was essential that the women were screened for PMS. Unlike previous reports, we also confirmed, during screening, that the women who participated in our study did not have dysmenorrheic pain secondary to pelvic pathology (secondary dysmenorrhea) but rather that they had severe (17) primary (4) dysmenorrhea. In addition, we assessed QoL at two randomized time-points during the menstrual cycle; with and without menstrual pain. Our results, therefore, support a direct link between menstrual pain and QoL.

We have confirmed that the painful menstrual cramps experienced by women with primary dysmenorrhea, substantially reduces QoL during menstruation each month. It is likely that treatment of dysmenorrheic pain may reverse these negative effects. Future studies should investigate whether QoL is restored with effective treatment.

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests related to the work in this manuscript.

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CHAPTER FOUR

Paper 3:

The 24 Hour Progression of Menstrual Pain in Women with Primary Dysmenorrhoea when given Diclofenac Potassium: A Randomised, Double-blinded, Placebo-controlled Crossover study

From: (ARCH) Paula Sonneveld [paula.sonneveld@springer.com]

Sent: 24 October 2013 02:13 PM

To: Stella Iacovides

Subject: Your Submission ARCH-D-13-00906R1

Dear Ms Stella Iacovides,

We are pleased to inform you that your manuscript, "The 24 hour progression of menstrual pain in women with primary dysmenorrhea when given diclofenac potassium: A randomized, double-blinded, placebo-controlled crossover study", has been accepted for publication in

Archives of Gynecology and Obstetrics.

Please remember to quote the manuscript number, ARCH-D-13-00906R1, whenever inquiring about your manuscript.

With best regards,

Paula Sonneveld

The 24 hour progression of menstrual pain in women with primary dysmenorrhea when given diclofenac potassium: A randomized, double-blinded, placebo-controlled crossover study.

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ABSTRACT

Purpose: Primary dysmenorrhea, which refers to painful, spasmodic cramping in the lower abdomen just before/or during menstruation, is the most common gynecological complaint in women of reproductive age. Non-steroidal anti-inflammatory drugs have been prescribed as the first-line therapy for pain relief from dysmenorrhea. We aimed to investigate the efficacy of the daily recommended dose (150mg) of diclofenac potassium, administered at set intervals across the first 24 hours of menstruation, in treating severe menstrual pain in 24 women with severe primary dysmenorrhea.

Methods: In a randomized, placebo-controlled, double-blind cross-over study, women rated their menstrual pain intensity on a 100-mm visual analog scale across set time intervals over a 24-hour period.

Results: Menstrual pain intensity was significantly reduced after taking the first capsule of diclofenac, and remained consistently lower ($P < 0.0001$), compared to initial pain intensity, in the morning (before treatment), throughout the day, evening and into the next morning. Also, women rated their pain intensity as significantly lower ($P < 0.001$) at each time point across the 24-h time interval of the cycle when receiving diclofenac compared to the cycle when they received placebo. No woman required rescue medication when taking diclofenac potassium compared to 6 women taking rescue medications during the placebo trial. When taking only placebo, women rated their menstrual pain intensity as persistently severe across the first 24 hours of menstruation.

Conclusion: These results show that the recommended daily dose of diclofenac potassium, in three 50 mg doses across the day and evening, offers effective menstrual pain relief across 24 hours, compared to placebo, in women with severe primary dysmenorrhea.

KEYWORDS

Dysmenorrhea, menstruation, diclofenac, pain, treatment

RUNNING TITLE

Diclofenac potassium is effective for menstrual pain relief

INTRODUCTION

Primary dysmenorrhea, defined as painful, spasmodic cramping in the lower abdomen, just before and/or during menstruation, in the absence of any discernable macroscopic pelvic pathology [1], is the most common gynecological condition among women of reproductive age [2,3]. The onset of primary dysmenorrhea usually occurs in adolescence, at or shortly after (6-24 months) menarche [4]. Primary dysmenorrheic pain is most severe during the first or second day of menstruation and typically lasts for 8-72 hours [3]. The pain may radiate to the back and thighs, and is frequently accompanied by systemic symptoms including nausea, vomiting, diarrhoea, fatigue and insomnia [4,5].

Prevalence estimates of this gynecological inflammatory disorder vary between 45 and 95% of menstruating women [6,7], and is very severe in approximately 10 - 25% of women of reproductive age [1,4,8,9]. The painful menstrual cramps may be considerably disabling; dysmenorrheic pain has been documented to be as intense as renal colic pain [10] and, as such, has been associated with decreased physical activity [11-13], recurrent short-term school or work absenteeism [2], interference with women's social and professional lives [14], and poor subjective [15,16] and objective sleep quality [17,18].

Primary dysmenorrhea is believed to result from excessive Prostaglandin (PG) $F_{2\alpha}$ release [1,5] which causes vasoconstriction of uterine blood vessels (uterine ischemia) and increased uterine smooth muscle contraction [4]. The contraction of the ischemic uterus is the likely cause of dysmenorrheic pain [19]. Furthermore, $PGF_{2\alpha}$ lowers the threshold for pain perception by sensitizing nerve endings to pain [4,5,20]. Non-steroidal Anti-Inflammatory Drugs (NSAIDs)

have been prescribed as the first-line therapy for pain relief from dysmenorrhea [5,13,20-22]. Pharmacologically, NSAIDs inhibit the iso-enzymes of the cyclooxygenase (COX) family which catalyze the synthesis of PGs from arachidonic acid. Cyclooxygenase exists primarily in two isoforms: COX-1 and COX-2, each with different prevalence and effects in various tissues [21,23]. Cyclooxygenase-1 is involved in a variety of regulatory and homeostatic functions such as cytoprotection of the gastric mucosa, [21,23] whereas COX-2 is primarily upregulated in numerous pathophysiological states by pro-inflammatory agents [21,23].

Historically, traditional NSAIDs, the selective COX-1 inhibitors, that inhibit COX-1 more than COX-2, such as naproxen and ibuprofen, and the non-selective COX inhibitors that inhibit both COX-1 and COX-2, such as diclofenac and piroxicam, [21,23] were prescribed to treat dysmenorrhea [24,25]. These traditional NSAIDs have analgesic efficacy superior to placebo for treating dysmenorrheic pain [14,26-34]. However, concerns over the gastrointestinal (GI) safety associated with the inhibition of COX-1 [5,21,35], led to the production of the “newer” generation NSAIDs (e.g. celecoxib, rofecoxib, and lumiracoxib) that are more selective and more specific in their inhibition of COX-2, while sparing COX-1 [21]. These “newer” NSAIDs were, until recently, prescribed to treat a variety of inflammatory conditions, including dysmenorrhea [5,20,36]. However, many of these COX-2 specific inhibitors have been withdrawn due to cardiovascular safety concerns [6,22,35].

As such, health care providers and women with dysmenorrhea have to now resort back to the “older” generation, non-selective COX inhibitors/NSAIDs to treat menstrual pain, with varying degrees of success. Therefore, there is still a need to identify which one of these non-selective

COX inhibitors/NSAIDs is best able to treat menstrual pain quickly and safely. One such NSAID that is proving to be beneficial in treating dysmenorrhea is diclofenac, a non-selective NSAID with a four-fold selectivity of COX-2 over COX-1 [21]. Its poor selectivity of COX-1, as well as its pharmacological properties which allow diclofenac to exert an extended duration of action, despite its rapid systemic elimination, mean that it has a low side-effect profile [21,23,37,38], rendering it a safe option for the treatment of the repetitive, acute pain experienced monthly by women with dysmenorrhea. Several studies have shown that diclofenac is an effective treatment for dysmenorrhea in the short-term, from two to eight hours after treatment administration [14,29,39]. Studies have varied in terms of daily doses being taken (from one to six times daily) [14,29,34,39,40] with most studies allowing participants to choose their own dosing schedule based on the need for pain relief [14,29,34,40]. To our knowledge, only one study, which was conducted by our research group, has monitored dysmenorrheic pain severity over a period of more than 8 hours with diclofenac potassium versus placebo [40]. In this study, pain intensity was measured before and 2 h after treatment (diclofenac, refecoxib, meloxicam or placebo) over a 2-to-3-day period. However, dosages were not consistent among women, as each woman was allowed to self-medicate with up to two pills daily [40].

In this study we aimed to investigate further the efficacy of the daily recommended dose of diclofenac potassium (150mg), administered as 50 mg capsules, at three intervals across the first day of menstruation, compared to placebo, in treating severe primary dysmenorrhea in a randomized, double-blind, crossover study. We assessed dysmenorrheic pain severity before

and after each capsule, as well as the following morning to determine the progression of pain across 24 hours with and without effective treatment.

METHODS

Screening phase

Thirty three women from a university student population volunteered to participate in the study, and gave written informed consent before participation. Ethical clearance was obtained from the University of the Witwatersrand's Committee for Research on Human Subjects, which adheres to the principles of the Declaration of Helsinki (Clearance no. M050537).

The volunteers were first interviewed and screened to ensure that they were generally healthy women with severe primary dysmenorrhea. A 100-mm visual analog scale (VAS) anchored from “no pain at all” to “the worst pain I have ever felt” was used to determine the severity of each volunteer's retrospective dysmenorrheic pain (over the last 6 months). The VAS has been shown to be a reliable and valid measure of experimental and clinical pain, which is sensitive to the effects of treatment of clinical pain and to small changes in pain intensity [41-45].

Women were asked to make a mark on the 100-mm VAS to indicate the intensity of their pain, and VAS scores were obtained by measuring the distance, in mm, between the beginning anchor point (“no pain at all”) to the mark filled in by the subjects. The VAS assessment of dysmenorrheic pain intensity is highly correlated with the pain rating index and the present pain index derived from the McGill pain questionnaire [40]. Women who rated their menstrual pain, for the last 6 months, above 60 mm on the VAS were considered to have severe

dysmenorrheic pain [46]. Women also completed a customized questionnaire about their menstrual cycles and history of menstrual pain, based on Andersch and Milsom (1982) [8]. They were asked about the impact of dysmenorrheic pain on daily activity, the presence of associated symptoms, and their analgesic requirements. Volunteers who had a history of pathological conditions associated with uterine pain, indicating secondary dysmenorrhea and not primary dysmenorrhea, were excluded from the study. In addition, volunteers were immediately excluded from the study if they presented with irregular menstrual cycles (defined as lasting < 21 days or > 35 days and/or with more than 4 days variation between cycles) [47], insufficient dysmenorrheic pain (< 60 mm on the VAS), or sensitivity to NSAIDs. For participation in the study, the women were required to have a history of primary dysmenorrhea, starting shortly after menarche [19], and were also required to be nulliparous individuals who were not taking chronic medication (including oral contraceptives) for at least six months before the study. In addition, the 30-item version of the General Health Questionnaire (GHQ) was used for psychological screening and only women who scored less than 6, indicating normal psychological status were included in the study [48]. After completion of the screening procedures, twenty-four eligible women with a history of primary dysmenorrhea agreed to participate in the study.

Procedures

The women were required to follow a randomized, double-blinded, placebo-controlled, crossover medicated procedure on the day they experienced their most intense dysmenorrheic pain. All women experienced their most severe dysmenorrheic pain on day 1; the first day of menstruation. Study medications were diclofenac potassium (50 mg, Cataflam D, Novartis,

South Africa) or placebo (cane sugar); disguised in identical gelatine capsules. The study was conducted over two menstrual periods, with each medication being taken in a separate menstrual period. Women were randomly assigned to a treatment sequence based on a Latin square design. 14 women had placebo first and the remaining 10 women had diclofenac potassium first. Each woman was provided with a diary in which to document menstrual pain severity, times of medication administration, adverse events, and details of any rescue medications taken. The protocol for treatment and pain severity evaluation is outlined in Figure 1. When the women first felt sufficient dysmenorrheic pain to require pain relief, they were instructed to record the time, as well as their pain intensity on a VAS anchored from “no pain at all” to “the worst pain I have ever felt”, before self-medicating with a prescribed capsule taken with a glass of water. The onset of dysmenorrheic pain for all the women was in the morning hours; therefore all the women took their first prescribed capsule in the morning, shortly after waking (between 8:00 and 10:00 am). Participants were instructed to rate their menstrual pain severity on a second VAS two hours after taking medication; an indication of any pain relief that the medication may have provided. Five hours after taking the first capsule, regardless of whether pain relief was required, the women completed a third VAS before taking the second prescribed capsule. Two hours after taking the second prescribed capsule, the women completed a fourth VAS; again serving as an indication of any pain relief provided by the medication. In the evenings, before going to sleep, the women completed a fifth VAS to indicate the intensity of their dysmenorrheic pain, and took the third prescribed capsule. All women went to bed between 21:00 and 23:00 pm. Thus the time interval between capsules 1 and 2 was always five hours, while the time interval between capsules 2 and 3 varied between

6 to 10 hours. Lastly, upon waking the following morning, the women rated the intensity of their current dysmenorrheic pain on another VAS.

In the event that any of the women required further pain relief from their dysmenorrheic pain during the day they were allowed to use their own rescue medication (that which they normally would take). However, the women were encouraged to try and not take rescue medication unless it was absolutely necessary. Such information was recorded and is reported in Table 2. However, regardless of whether the women took rescue medication or not, they were still expected to complete the prescribed capsule administration as described in the research procedure above. When the women required further pain relief from their dysmenorrheic pain during the night, however, they were given another (fourth) prescribed capsule (50 mg diclofenac potassium or placebo), and were encouraged to take the prescribed capsule before resorting to their own rescue medication (see Table 2).

Statistical Analyses

All data were analyzed using STATISTICA (StatSoft, Tulsa, version 5, 1996). A two-tailed probability of $P < 0.05$ was considered to be statistically significant. All VAS measurements (in mm), used to describe dysmenorrheic pain, were normalized before statistical analyses using the arcsine transformation; as advised when a large number of values fall within the extremes of the scale [49]. However all text and graphs report the VAS data as back transformed values (in mm). The standard deviations of back transformed data are asymmetric. However, only the standard deviation values above the mean are presented All VAS data are thus expressed as mean $\pm$ standard deviation (SD).

Each woman's 24-h progression of dysmenorrheic pain intensity (VAS) scores were plotted on separate graphs and best-fit curves were fitted (Table curve 2D, version 3 for Win 32, Jandel Scientific Software, AISN Software Inc., San Rafael, CA). Area under the VAS-time curve (AUC, mm.h⁻¹) was calculated and a paired t-test was used to compare the AUC between treatments (diclofenac versus placebo, n = 24).

A two-way repeated-measures analysis of variance (two-way RM-ANOVA) with time and treatment administered as main effects, was used to compare the intensity of dysmenorrheic pain, as measured by the VAS (mm), between the treatments (diclofenac versus placebo, n = 24), across the various times of assessment over the 24h period. Where appropriate, the Student-Newman-Keuls (SNK) post-hoc test was used to assess the origin of any significant differences detected by the ANOVA model.

The McNemar's test was used to determine whether the number of women who took rescue medication during diclofenac treatment versus placebo was statistically significant.

A secondary analysis using the same statistical procedures described above was performed on the group of women who did not use rescue medication on any occasion during the 24-hour placebo treatment (n = 18) to evaluate the true placebo effect on dysmenorrheic pain.

RESULTS

The characteristics of the twenty-four women who participated in the study are shown in Table 1.

All of the women followed and completed the study medication procedure; however, six of the twenty-four women opted to take rescue medication when placebo failed to provide pain relief. The rescue medications taken, as well as the dose and time at which they were taken, are displayed in Table 2.

Table 1. Characteristics of the 24 women who participated in the study

	Women with dysmenorrhea (n = 24)
Age (years)	20 $\pm$ 2
Weight (kg)	59.1 $\pm$ 8.0
Height (m)	1.6 $\pm$ 0.1
Body Mass Index (kg/m ²)	22.9 $\pm$ 2.8
Age of onset of menses (years)	12 $\pm$ 2
Age of onset of dysmenorrhea (years)	13 $\pm$ 1
Positive family history of dysmenorrhea (number)	21
Number of years of menstruation	8 $\pm$ 3
Usual menstrual cycle length (days)	28 $\pm$ 2
Usual menstruation phase length (days)	5 $\pm$ 1
Average menstrual pain intensity (for previous 6 months; VAS, mm)	76 $\pm$ 13

Data are expressed as mean $\pm$ SD.

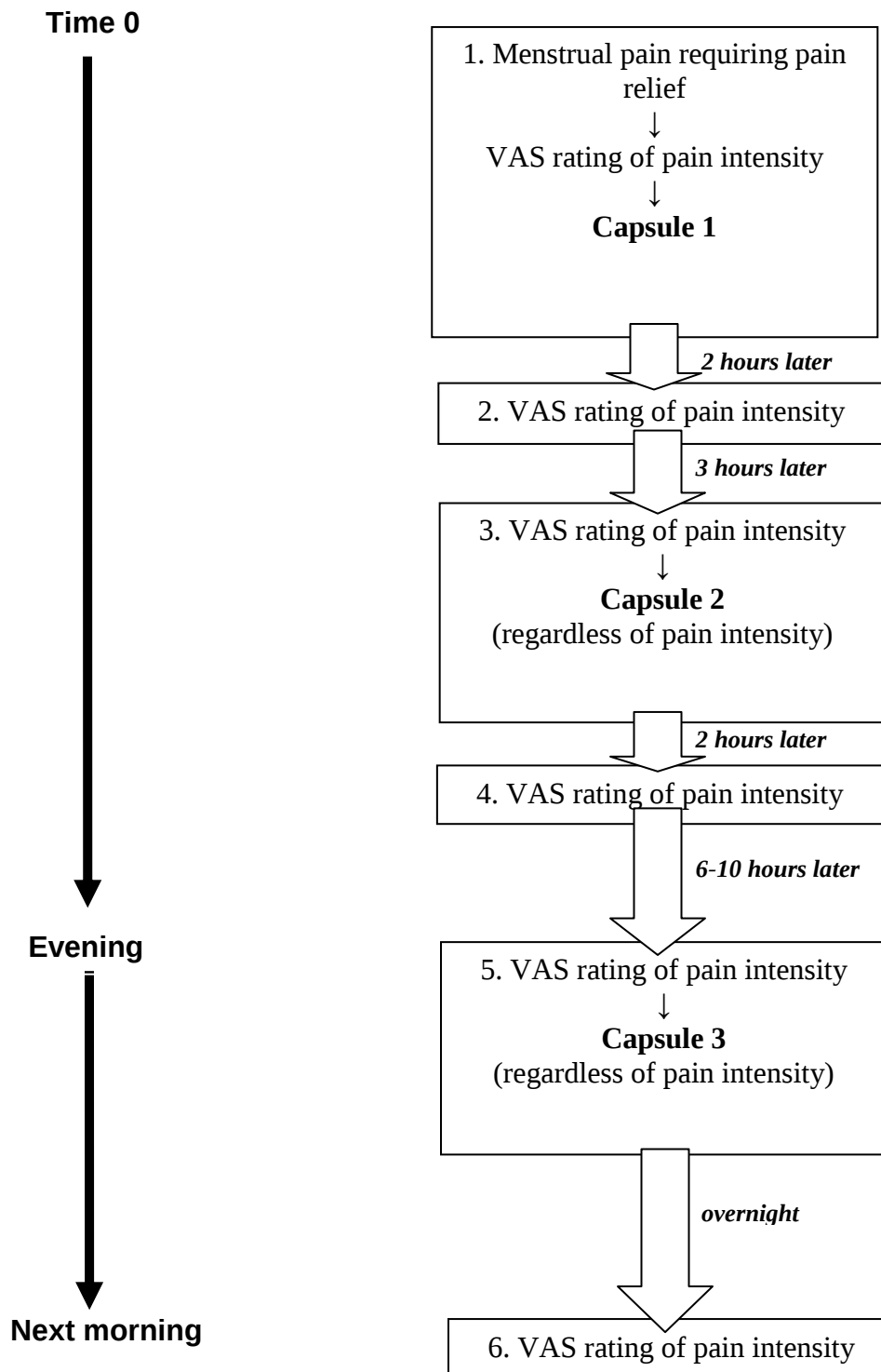


Figure 1. An outline of the study's protocol. Each woman ($n = 24$) completed steps 1 to 6 by taking placebo during one menstrual cycle and diclofenac during another menstrual cycle, in a randomized double blind order.
VAS = visual analog scale

Table 2. Details, including dosage and time, of the rescue medications taken by 6 women during the placebo arm of the study

Subject	Rescue Medication Taken	Dosage (mg)	Time of day taken
1	Ibuprofen Ibuprofen Ibuprofen	400 400 400	10:00 14:00 23:30
2	Combined: Paracetamol Ibuprofen Combined: Paracetamol Ibuprofen	1000 200 1000 200	07:00 14:00
3	Paracetamol	1000	10:00
4	Combined: Ibuprofen Paracetamol Codeine Phosphate	200 350 10	14:45
5	Naproxen	220	13:15
6	Ibuprofen	400	15:30

Six of the twenty-four women with primary dysmenorrhea required rescue medications when placebo failed to provide pain relief. No rescue medications were taken when the women's dysmenorrheic pain was treated with diclofenac potassium.

The progression of dysmenorrheic pain intensity, expressed as the average VAS scores, throughout the day when the women were taking diclofenac potassium compared to placebo (including the six women who took rescue medications) is displayed in Figure 2. A two-way RM-ANOVA revealed significant treatment [$F(5,115) = 31.27, P < 0.0001$], time [$F(1,23) = 32.60, P < 0.0001$], and treatment-time interaction [$F(5,115) = 8.47, P < 0.0001$] effects. As demonstrated by the starting points of the two curves in Figure 2 (Time “0”), the women’s intensity of dysmenorrheic pain before any treatment was not significantly different between the two trials (diclofenac versus placebo; $P = 0.90$). The progression of pain intensity throughout the day, as shown in Figure 2, followed two distinct patterns, depending on the treatment received (diclofenac or placebo). As confirmed by post-hoc analyses, the pain intensity of the women taking diclofenac potassium was significantly reduced after taking capsule 1, and remained at a significantly lower intensity at all the time points compared to the initial (Time “0”) pain intensity (SNK: $P < 0.0001$ between Time “0” and all subsequent time-points; Figure 2). In addition, women rated their pain intensity as significantly lower when taking diclofenac potassium compared to placebo at each time point after commencing treatment (after Time “0”) ($P < 0.0001$; Figure 2). When the women were taking placebo, pain intensity was significantly lower at 7 hours (after capsule 2; SNK: $P = 0.001$) and in the morning (SNK: $P = 0.0007$) compared to Time “0”.

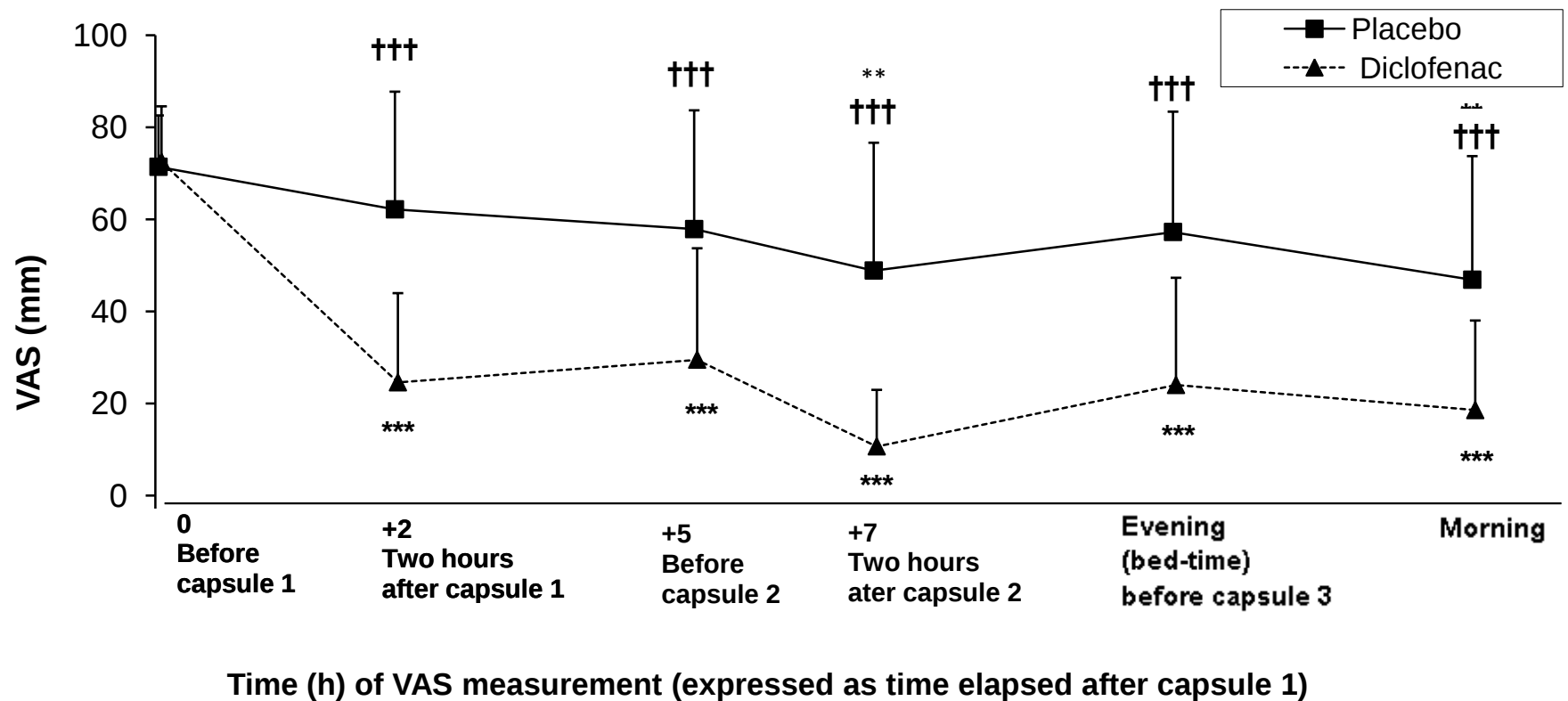


Figure 2. The progression of dysmenorrheic pain intensity over time, as measured by the Visual Analog Scale (back transformed VAS mean and SD) when the 24 women with primary dysmenorrhea were given either diclofenac potassium or placebo (including the 6 women who took rescue medications as shown in Table 2). Pain intensity was assessed at six different time points across 24 hours; before taking capsule 1 (Time = 0), two hours after taking capsule 1 (Time = +2), before taking capsule 2 (Time = +5), two hours after taking capsule 2 (Time = +7), in the evening before going to bed (before taking capsule 3), and in the morning upon waking.

* represents a significant difference in the VAS score from the initial VAS score (before treatment at Time = 0): * $P < 0.05$, ** $P < 0.01$, *** $P < 0.0001$.

† represents a significant difference in the VAS score between diclofenac potassium and placebo at each time point: ††† $P < 0.0001$.

Furthermore, the area under the VAS-time curve (mm.h^{-1}) was significantly greater when the women were taking placebo compared to when they were taking diclofenac potassium ($t(23)=8.48$; $P < 0.0001$), indicating that the women rated the intensity of their dysmenorrheic pain as more severe throughout the 24-h assessment period when they were taking placebo (including those women who used rescue medications) compared to when they were taking diclofenac potassium.

Results were similar when the 6 women who took rescue medication were excluded from the analysis. The two-way RM-ANOVA between diclofenac and placebo alone ($n=18$), showed significant treatment [$F(1,34) = 29.5$, $P < 0.0001$], time [$F(5,170) = 30.5$, $P < 0.0001$] and interaction [$F(5,170) = 11.4$, $P < 0.0001$] effects. SNK post hoc analyses showed that following treatment with the first capsule, the pain ratings after the administration of diclofenac potassium were significantly lower than after placebo administration ($P < 0.0001$) at all time points. The placebo response for dysmenorrheic pain over the first 24 hours of menstruation is shown in Figure 3. Pain severity was lower from 5 hours after taking the first capsule onwards, compared to before taking the first capsule although pain ratings remained, on average, at or above a severe level (60 mm) for the 24 hour period.

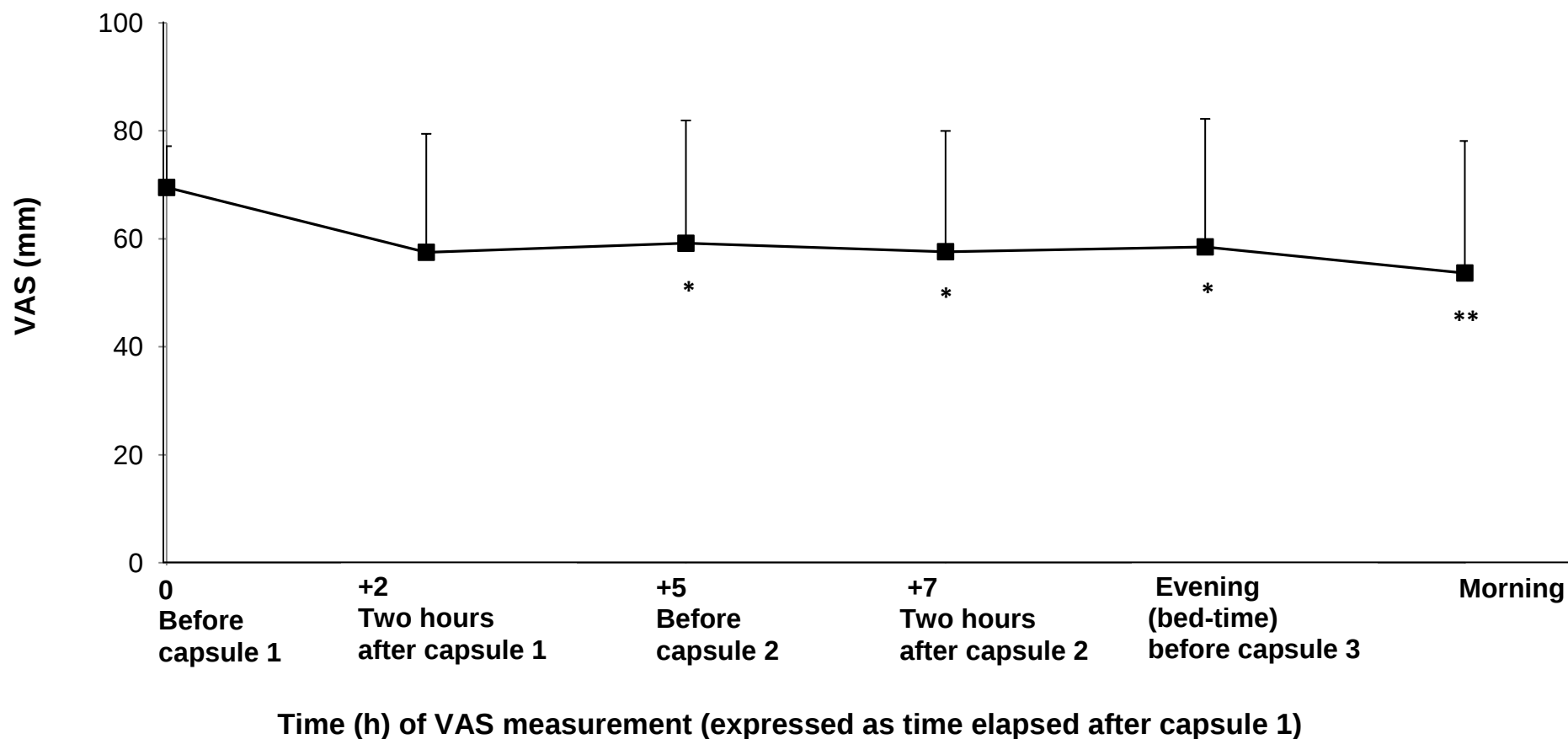


Figure 3. The progression of dysmenorrheic pain intensity over time, as measured by the Visual Analog Scale (back transformed VAS mean and SD) when 18 women with primary dysmenorrhea were treated with placebo and resisted taking any rescue medications. Pain intensity was assessed at six different time points across 24 hours; before taking capsule 1 (Time = 0), two hours after taking capsule 1 (Time = +2), before taking capsule 2 (Time = +5), two hours after taking capsule 2 (Time = +7), in the evening before going to bed (before taking capsule 3), and in the morning upon waking.

* represents a significant difference in the VAS score from the initial VAS score (before treatment at Time = 0): * $P < 0.05$, ** $P < 0.01$

No rescue medications were taken when the women's dysmenorrheic pain was treated with diclofenac potassium, and no woman took the fourth capsule of diclofenac potassium during the night. In addition, there were no reported adverse events when the women were taking diclofenac potassium, placebo or rescue medications for their menstrual pain.

DISCUSSION

We have shown that diclofenac potassium, administered in three 50 mg doses across a day, effectively attenuated menstrual pain throughout the day and night, and into the following morning compared to placebo in women experiencing severe dysmenorrhea. None of the women required rescue medication when they treated their dysmenorrheic pain with diclofenac potassium, whereas 6 of them (25%) used rescue medication when taking placebo. The 150-mg recommended daily dose of diclofenac potassium is therefore effective in treating dysmenorrheic pain.

Pharmacologically, NSAIDs are prescribed as the agent of choice to treat dysmenorrhea [5,13,20-22], as they are able to effectively inhibit the COX-2 enzyme responsible for the production of PGs implicated in the etiology of dysmenorrhea. Since the withdrawal of the once-thought safer “newer” generation COX-2 selective and COX-2 specific NSAIDs from the market [6,22,35], the traditional “older” generation non-selective COX-inhibitors/NSAIDs, such as diclofenac and ibuprofen, are now being prescribed more frequently to safely treat dysmenorrhea. We have shown that the “older” generation non-selective COX inhibitor, diclofenac, is effective in treating dysmenorrheic pain.

Our study results are in agreement with several other studies that have shown that diclofenac (sodium and potassium) is effective in alleviating dysmenorrheic pain. Compared to placebo, 25 mg of diclofenac sodium, administered three times daily, was found to significantly reduce menstrual pain in 35 women with dysmenorrhea [34]. However, in this study pain assessment was only done once after menstruation and women were asked to compare current pain intensity to that of the previous menstruation, requiring retrospective recall [34]. Others have reported diclofenac sodium (50 mg up to three times daily, when needed) to be more effective and more tolerable in the treatment of dysmenorrhea, compared with a smooth muscle relaxant, at least during a 2-h assessment following first treatment [14]. Similarly, diclofenac dispersible (equivalent to 50 mg diclofenac sodium) taken up to four times daily was found to provide menstrual pain relief superior to placebo over a 6-h period [29]. In addition, a single dose of aceclofenac (100 mg), a glycolic acid ester of diclofenac [50], used either alone [28], or in combination with a smooth muscle relaxant [51], has been reported as a safe and well-tolerated analgesic for primary dysmenorrhea.

Similarly, diclofenac potassium has been found to be highly effective in relieving menstrual pain in 11 women with primary dysmenorrhea [40]. In this study, a maximum of two capsules of diclofenac potassium (50 mg) was prescribed daily and pain assessment done immediately before and two hours after taking the capsule [40]. Other studies have investigated the efficacy of diclofenac in the treatment of dysmenorrhea, however, they have been excluded from “The Cochrane Collaboration” [52], either due to lacking of randomization or lack of blinding, and are thus, not discussed here.

Substantiating the efficacy of diclofenac potassium, via effective pain relief, we previously have reported that diclofenac potassium restores the dysmenorrheic pain-induced reduction in physical activities [39] and dysmenorrheic pain-induced reduction in sleep quality [18]. Our data extend these findings to show that diclofenac potassium, when taken at three time-points across the day, provides effective treatment of severe dysmenorrheic pain across the day and through the night, such that pain intensity is lower across 24 hours, compared to placebo. We chose to instruct participants to take three capsules of medication across the day regardless of their level of dysmenorrheic pain at the time. We therefore cannot comment whether a lower dose over a 24 hour period might also be effective. Direct comparisons, however, with other studies are also difficult to make due to the varied doses (from one to six times daily) [14,29,34,39,40], the freedom of participants to choose their own dosing schedule based on the need for pain relief [14,29,34,40], and the fact that most studies only monitored pain for two to eight hours after treatment administration [14,29,39].

It has been previously recommended that treatment of primary dysmenorrhea with NSAIDs, in adolescents at least, could be initiated one to two days before the onset of menstruation [20]. We have shown that taking the recommended daily dose of diclofenac potassium, in three capsules across the first day of menstruation is an effective method to alleviate menstrual pain for at least 24 hours. The protocol employed by this study may be a better option given that the duration of treatment with NSAIDs for primary dysmenorrhea is recommended to be no longer than three days, to avoid possible adverse effects [22].

As described above, most research on the use of diclofenac for the treatment of dysmenorrhea has used diclofenac sodium. Although pharmacokinetic studies show similar bioavailability between diclofenac sodium and potassium, the mean time to reach maximal plasma levels is shorter with diclofenac potassium (± 30 minutes) [53] compared with diclofenac sodium (± 1.5 to 2 hours) [37]. Such properties may account for a faster onset of action with diclofenac potassium; for example diclofenac potassium significantly reduced postoperative dental pain intensity scores starting at 15 minutes, compared to diclofenac sodium at 2 hours [54]. However, no studies have directly compared the time efficacy of diclofenac potassium and diclofenac sodium in alleviating primary dysmenorrheic pain specifically.

Most previous investigations of efficacy of agents in treating primary dysmenorrhea have been conducted on less-selected, and in some cases, larger cohorts, than ours. Our study group was a non-clinical sample of young women recruited from a University population. As such, our results may not be generalizable to all adolescents and women with primary dysmenorrhea. A limitation of our study was the small sample size. However, each woman acted as her own control, which allowed for a more robust within-subject analysis to be performed. Despite the reduced statistical power sensitivity associated with a small sample size, we were still able to detect robust significant findings in the VAS pain ratings in the ANOVA model. The women in our study reported no adverse effects during or after administration of diclofenac potassium. However, our study was not intended nor powered to detect adverse events. It would take a far greater cohort to resolve differences in adverse effects associated with COX inhibitors taken for 2 days every month, by otherwise-healthy young women. Although not specifically in dysmenorrheic patients, the safety and tolerability of diclofenac has been reported in an

extensive review of worldwide clinical trials involving over 100 000 patients who were treated with diclofenac [55, 61]. Given that GI issues are generally of less concern in acute use of NSAIDs compared to chronic use [22,56], and given diclofenac potassium's poor selectivity of COX-1 [21], it is a safe GI option for the treatment of the acute pain experienced monthly by women with dysmenorrhea.

Our study is in agreement with most studies in that we found an NSAID to be superior to placebo in alleviating dysmenorrheic pain. Almost all randomized control trials investigating NSAIDs for the treatment of dysmenorrhea have reported a superiority of the active treatment compared to placebo [22,26-33,40,52]. In agreement with other studies [14,39,40], the women who received diclofenac potassium did not require rescue medication during the day or night. In comparison, six of the women chose to self-medicate with their preferred rescue medication when they were given placebo for their menstrual pain (Table 2). The removal of these 6 women from the statistical analysis revealed that diclofenac potassium offered superior pain relief to placebo at each time point across the 24-hour assessment period and also showed the daily progression of dysmenorrheic pain when women were taking placebo alone (Figure 3).

Little is known about the daily progression of dysmenorrheic pain. All 24 women in our study reported a morning onset of severe menstrual pain, which coincided with the beginning of menstruation. The onset of menstruation of the women in our study coincides with data showing that the majority of women ($\pm 54\%$) start menstruating in morning, while $\pm 32\%$ starting in the afternoon and early evening, and only about $\pm 14\%$ starting during the night [57]. In terms of the onset of pain, however, our study's findings are in contrast with a report showing increased

primary dysmenorrheic pain during the evening, coinciding with reduced uterine blood flow during the evening [58]. Since the main factors attributed to the etiology of primary dysmenorrheic pain, namely: prostaglandins, vasopressin, and uterine blood flow and contractility, have all been found to display diurnal variation [59,60], it is plausible that dysmenorrheic pain may also have a diurnal rhythm. However, our analysis of dysmenorrheic pain severity in women treated only with placebo revealed only a small decrease in pain severity 5 hours after the first capsule, which then remained at a constantly severe level (60 mm, on average) for the remainder of the 24 hour assessment period. More studies, on larger samples however, should be conducted to further investigate the daily variation in dysmenorrheic pain.

Primary dysmenorrhea in women of child-bearing age is extremely common, and the pain is often poorly-managed and debilitating [10]. We have shown that the recommended daily dose of a readily-available NSAID, diclofenac potassium, in 50 mg doses across the day and evening offers effective menstrual pain relief that lasts throughout the day, evening and into the next morning, compared to placebo.

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CHAPTER FIVE

Paper 4:

*Diclofenac Potassium Restores Objective and Subjective measures of
Sleep in Women with Primary Dysmenorrhoea*

Diclofenac Potassium Restores Objective and Subjective Measures of Sleep Quality in Women with Primary Dysmenorrhea

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Study Objectives: Primary dysmenorrhea is a common gynecological disorder that disrupts daytime functioning and nighttime sleep quality. We determined the effectiveness of diclofenac potassium, compared to placebo, in alleviating nighttime pain and restoring sleep architecture in women with primary dysmenorrhea.

Design: Randomized, double-blind, crossover study

Setting: Sleep laboratory

Participants: Ten healthy women (21 ± 1 years) with a history of primary dysmenorrhea.

Interventions: Placebo or diclofenac potassium (150 mg per day) for menstrual pain.

Measurements and results: We assessed objective measures of sleep (polysomnography) and subjective measures of sleep quality, mood, and intensity of menstrual pain. Compared to a pain-free phase of the menstrual cycle (mid-follicular), women receiving placebo for their menstrual pain had a poorer mood ($P < 0.01$), decreased sleep efficiency ($P < 0.05$), less REM sleep ($P < 0.05$), more stage 1 sleep ($P <$

0.01), and more sleep stage changes per hour of sleep during the night. Administration of diclofenac potassium compared to placebo not only attenuated the women's menstrual pain ($P < 0.05$), but also increased sleep efficiency ($P < 0.05$) and percentage of REM sleep ($P < 0.01$), decreased percentage of stage 1 sleep ($P < 0.05$) and number of sleep stage changes per hour of sleep ($P < 0.05$), and improved subjective ratings of sleep quality and morning vigilance ($P < 0.05$).

Conclusion: Diclofenac potassium effectively attenuates nighttime dysmenorrheic pain and restores subjective and objective measures of sleep quality to values recorded in a pain-free phase of the menstrual cycle.

Keywords: Primary dysmenorrhea, pain, sleep, diclofenac potassium, polysomnography

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PRIMARY DYSMENORRHEA IS DEFINED AS PAINFUL UTERINE CRAMPING IN THE LOWER ABDOMEN, JUST BEFORE OR DURING MENSTRUATION, IN THE ABSENCE of any discernible macroscopic pelvic pathology.^{1,2} Dysmenorrheic pain is most severe during the first or second day of menstruation and typically lasts for 8–72 hours.³ The pain may radiate to the back and thighs, and is frequently accompanied by systemic symptoms including nausea, vomiting, diarrhea, lack of energy and insomnia.⁴ Primary dysmenorrhea is a common disorder, affecting over 50% of menstruating women, and is very severe in approximately 10% to 15% of women of reproductive age.^{1,2,5} The prevalence of primary dysmenorrhea is reduced with increasing age; the pain has been found to improve in the third decade of a woman's reproductive life, and is also reduced after childbirth.^{1,5,6} Dysmenorrheic pain may be disabling and often results in school and work absenteeism, thus resulting in severe educational and economic consequences.^{3,5}

Our group previously investigated the impact of dysmenorrheic pain on subjective sleep quality and polysomnographic measures of sleep.⁷ Women with dysmenorrhea had a poorer subjective sleep quality; reduced sleep efficiency; more time awake, moving and in light stage 1 sleep (combined); and less

REM sleep compared to when they were in a pain-free phase of their menstrual cycle, and compared to women without menstrual-associated problems.^{7,8} Given the reciprocal relationship between sleep and pain,^{9–15} dysmenorrheic pain may not only disrupt quality of sleep, but these sleep disturbances and associated fatigue may accentuate the pain and its impact on daytime performance and mood.⁹

Dysmenorrheic pain is believed to result from excessive prostaglandin (PG) release, particularly $\text{PGF}_2\alpha$.^{1,2,5} As progesterone concentrations fall before menstruation, arachidonic acid is released from the endometrial cell membranes and a cascade of PG synthesis is initiated in the uterus.⁴ In comparison to women with eumenorrhea, women with dysmenorrhea have higher concentrations of $\text{PGF}_2\alpha$ in their menstrual fluid.¹⁴ $\text{PGF}_2\alpha$ causes potent vasoconstriction of the uterine blood vessels and myometrial contractions, both of which reduce blood supply to the uterus.¹⁵ The resultant uterine muscle ischemia and hypoxia are believed to be the origin of pain in primary dysmenorrhea.⁵ There is also evidence that $\text{PGF}_2\alpha$ lowers the threshold for pain perception by sensitizing nerve endings to pain.^{4,5,15} Thus, during menstruation, excessive release of PGs by the endometrium results in hypercontractility of the uterus and subsequent uterine muscle ischemia and hypoxia.⁷ The contraction of the ischemic uterus is the likely cause of dysmenorrheic pain. Given the involvement of PGs in the etiology of dysmenorrhea, the current most accepted approach for its treatment is to inhibit the synthesis of PGs.¹⁵

Nonsteroidal anti-inflammatory drugs (NSAIDs) are classified as PG synthetase inhibitors,^{16–18} and they function to inhibit cyclooxygenase (COX), the enzyme responsible for the forma-

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tion of PGs such as $\text{PGF}_2\alpha$. A recent study in our laboratory has found that the NSAID, diclofenac potassium, a nonselective COX inhibitor, is extremely effective in alleviating dysmenorrheic pain with no reported side effects during the course of the study.¹⁹ Diclofenac potassium has also been shown to be effective in restoring exercise performance in women with dysmenorrhea.²⁰ Although the negative effects of dysmenorrhea on sleep architecture have been documented,⁷ no study has investigated whether treating the pain is associated with an improvement in sleep quality.

The aim of our study, therefore, was to determine the effectiveness of diclofenac potassium compared to placebo in alleviating nighttime pain and sleep disruption in young women with primary dysmenorrhea.

METHODS

Subject Recruitment

Twenty-three women from a university student population volunteered to participate in the study, and gave written informed consent before participation. Ethical clearance was obtained from the University of the Witwatersrand's Committee for Research on Human Subjects, which adheres to the principles of the Declaration of Helsinki (Clearance no. M050537).

Volunteers were first interviewed and screened using comprehensive questionnaires to ensure that they fulfilled the inclusion criteria. The impact of dysmenorrheic pain on daily activity, the presence of associated symptoms, and the analgesic requirements of each woman were evaluated. For participation in the study, the women were required to have severe dysmenorrheic pain, with a history of primary dysmenorrhea, starting shortly after menarche.² Severity of dysmenorrheic pain was determined based on each woman's perception of her pain. Women were asked to make a mark on a 100-mm visual analogue scale (VAS) anchored from "no pain at all" to "the worst pain I have ever felt" to indicate the intensity of dysmenorrheic pain. VAS scores were obtained by measuring the distance, in mm, between the beginning anchor point ("no pain at all") to the mark filled in by each subject. Women who rated their menstrual pain > 60 mm on the VAS were considered to have severe dysmenorrheic pain.²¹ The women were also required to be nulliparous individuals, who were generally healthy and not taking any chronic medication (including oral contraceptives) for at least 6 months before the study. Exclusion criteria were pathological conditions associated with uterine pain (indicating secondary dysmenorrhea); chronic diseases, including gastrointestinal, sensory, autoimmune, mood, muscular, bone or joint disorders, asthma, and diabetes; irregular menstrual cycles; insufficient dysmenorrheic pain; a history of sensitivity to NSAIDs; irregular sleep-wake cycles; and signs of psychological disorders such as depression. The Pittsburgh Sleep Quality Index (PSQI)²² was used to screen for sleep disturbances; it is a self-rated measure of sleep quality over a one-month period and assesses variables including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. A global PSQI score > 5 indicates poor sleep quality; only women who scored ≤ 5 on the global PSQI were included in the screening phase of the study. The 30-item version of the General Health Question-

naire²³ was used for psychological screening, and only women who scored < 6 , indicating normal psychological status, were included in the screening phase of the study.

Screening Phase

Fifteen volunteers fulfilled all of the necessary criteria and participated in the screening phase; a month-long period during which subjects prospectively rated the severity of their dysmenorrhea, premenstrual symptoms (PMS), and sleep-wake schedules. Severity of dysmenorrhea was evaluated for every day of menstruation using a 100-mm VAS, anchored from "no pain at all" to "the worst pain I have ever felt." Only women scoring > 60 mm on the VAS on at least one day of menstruation were eligible for the recording phase of the study. During the month-long screening phase, the sleep-wake schedules of the women were assessed using sleep-wake diaries. Information from sleep diaries was used to confirm that the women had regular sleep-wake patterns and to schedule times for lights-out for the women's overnight recordings. To evaluate symptoms of PMS, the women completed the Penn Daily Symptom Rating Form,²⁴ a validated rating scale for PMS, over one menstrual cycle. One woman scored > 80 on the Daily Symptom Rating in her late-luteal phase, with an increase of more than 50% from the postmenstrual score, indicating significant PMS; she was therefore excluded from the study. Another woman was excluded because of irregular sleeping patterns. Two other women were removed from the study because they chose to begin oral contraceptive administration to control their dysmenorrheic pain, while another woman de-registered from the university and voluntarily withdrew from the study. Ten women were therefore eligible to participate in the study. Four women were white and 6 women were black. The physical characteristics and menstrual cycle history of the 10 subjects who completed the study are shown in Table 1.

Study Procedures

Following the screening phase, subjects were scheduled for an adaptation night in the Wits Dial-a-bed Sleep Laboratory to familiarize them with the experimental procedures. The adaptation night always took place 2-to-3 nights before the first recording night, and subjects were required to be in a pain-free phase of their menstrual cycle. The women returned to the laboratory over 2-to-3 menstrual cycles for 3 overnight recordings: once during the mid-follicular phase (no-pain trial) and twice during menstruation (pain trials). The 2 pain trials occurred during different menstrual cycles.

As determined from their menstrual history, subjects spent their pain trials in the sleep laboratory in the early follicular phase of their menstrual cycle (during menstruation). All subjects had their pain trials on the night of the first day of their menstrual bleeding (day 1), which was when they experienced their most severe menstrual-associated pain. The no-pain trial took place in the mid-follicular phase of the menstrual cycle between days 6 and 10. Subjects were randomly, and in a double-blind fashion, given diclofenac potassium (Cataflam, Novartis, Johannesburg, South Africa) in one pain trial (Pain/Diclofenac), and placebo (sugar pill) in the other pain trial (Pain/Placebo). In the no-pain trial, subjects were given diclofenac potassium

(No-Pain/Diclofenac) to control for any ambiguous effects that diclofenac potassium might have on sleep independent of its pain-relieving effects during menstruation.

On the day preceding each recording night, subjects were asked not to nap or participate in strenuous exercise and to abstain from caffeinated food or beverages for at least 8 hours before bedtime. On all nights subjects went to bed at their customary bedtimes and slept in a sound-attenuated, temperature-regulated bedroom in the sleep laboratory.

To confirm that subjects had ovulatory menstrual cycles, they were each provided with a commercially available self-test kit, which detects the presence of luteinizing hormone (LH) in urine (Clearplan, Unipath, Bedford, England). All subjects were confirmed as having ovulatory cycles before having their sleep recorded for at least one of their pain trials.

Medication

Subjects were given 2 prescribed capsules to take during the day preceding the sleep recordings and a third capsule to take before going to bed. Each capsule consisted either of 50 mg of diclofenac potassium or placebo, disguised in identical gelatin capsules. The women therefore took the recommended daily dose of diclofenac potassium (150 mg). During the pain trials, the subjects took their first prescribed capsule when they felt they had enough pain to require pain relief (before 09:00 for all subjects). The second prescribed capsule was taken 5 hours later, and the final capsule 30 minutes before bedtime, regardless of whether they required pain relief.

The subjects were required to follow a similar standard procedure throughout the day for the no-pain trial. Since the subjects would not be experiencing menstrual pain, the time that subjects took the first capsule (50 mg diclofenac potassium) was standardized to 10:00. Five hours later, at 15:00, the subjects took the second prescribed capsule, and they took the final capsule 30 minutes before going to bed. The women were questioned about any side effects that they experienced when taking the medications; none of the subjects reported any side effects.

If the subjects required further pain relief after taking the study medication, they were allowed to take their own rescue medication. Six subjects required rescue medication during the day of their Pain/Placebo trial. However, only one subject took rescue medication less than 6 hours before lights-out on the Pain/Placebo trial; the subject chose to take 400 mg of ibuprofen shortly after going to bed. None of the women took rescue medication during the Pain/Diclofenac trial.

Data Acquisition and Analysis

Polysomnographic Recordings

Subjects arrived at the sleep laboratory at least 2 h before bedtime for preparation for overnight polysomnography (PSG). The PSG recordings included: electroencephalographic (EEG), electroculographic (EOG), and electromyographic (EMG) recordings. Electrodes for EEG recordings were placed at C3 and C4 according to the international 10-20 system²⁵ and were referenced to A1 and A2. EEG signals were digitized at a sampling rate of 200 Hz, high-pass filtered at 0.3 Hz, and low-pass fil-

Table 1—Subject Characteristics and Details of Menstrual Cycle History

Subject Characteristics	Women with dysmenorrhea
Age (years)	21 ± 1
Weight (kg)	56.6 ± 6.5
Height (m)	1.62 ± 0.04
Body mass index (kg/m ²)	21.6 ± 2.5
Age at onset of menses (years)	13 ± 1
Age at onset of primary dysmenorrhea (years)	14 ± 2
Usual menstrual cycle length (days)	28 ± 2
Usual menstruation phase length (days)	5 ± 1
Intensity of dysmenorrheic pain on the VAS during the screening phase (mm)	71 ± 20

Data expressed as mean ± SD (n = 10)

tered at 30 Hz. Recordings were made on a computerized EEG system (Cadwell Easy EEG, version 2.0.2, Cadwell Laboratories Inc, Kennewick WA).

Thirty-second epochs were scored according to standard criteria²⁵ by one scorer (SI) who was blind to the identity, menstrual cycle phase, and treatment of the subject. A second experienced scorer randomly scored one-third of the records. Agreement between scorers was > 85%.

Time in bed (TIB) signifies the time in minutes between lights-out and lights-on. Sleep onset latency (SOL) was taken as the time (minutes) from lights-out to the first epoch scored as stage 2 sleep. The total sleep time (TST) was determined as the time, in minutes, from SOL to lights-on minus in-bed wakefulness. The time between sleep onset and the first sign of REM sleep was recorded as REM sleep onset latency.²⁵ The latency to slow wave sleep (SWS) was taken as the time (minutes) from sleep onset to the first epoch of stage 3 sleep. Movement time (MT) signifies the time that subjects were moving during sleep, as defined by Rechtschaffen and Kales.²⁵ Time spent in each sleep stage was calculated as a percentage of TST for each recording. Sleep efficiency (SE) was calculated as TST divided by TIB and expressed as a percentage.

Subjective Ratings

A 100-mm VAS, anchored at "no pain at all" and "the worst pain I have ever felt," was used to assess the intensity of dysmenorrheic pain. The VAS was completed in the morning on the first day of menstruation, before administration of either diclofenac potassium or placebo, and then again approximately 30 min before going to bed. In addition, the following morning, the women were asked to use the VAS to rate their intensity of menstrual pain and to recall the intensity of pain experienced during the night.

The Profile of Mood States (POMS) questionnaire was used to assess each woman's mood in the evening before going to bed. The POMS is a validated questionnaire consisting of 65 adjectives that measure how a person is feeling.²⁶ A total mood score for each subject was calculated from the POMS by summing the negative mood scores, subtracting the vigor score, and adding a constant of 100 to avoid negative scores.

After each recording night, subjects assessed their preceding night's sleep quality on a 100-mm VAS, with anchor points from "no sleep" to "best sleep I have ever had." They also assessed their morning vigilance on a 100-mm VAS, with anchor points from "not at all alert and fresh" to "most alert and fresh I have ever felt."

Statistical Analysis

Data were analyzed using Instat (GraphPad Software Inc., version 3, 1997). A 2-tailed probability of $P < 0.05$ was considered to be statistically significant, and all data are expressed as mean $\pm$ SD. All VAS measurements (in mm) were normalized before statistical analysis using the arcsine transformation. However, in the results, all the VAS data are reported as back-transformed values.

A repeated measures analysis of variance (RM-ANOVA), with a Tukey post hoc test, was used to detect differences in PSG sleep variables, total mood (POMS) scores, and subjective measures of sleep quality and morning vigilance for the 3 trials (No-Pain/Diclofenac, Pain/Diclofenac, and Pain/Placebo). Effect size calculations were made to compare the effectiveness of diclofenac versus placebo in the 2 pain trials using Cohen's d , calculated as the difference between the 2 means divided by the pooled standard deviation. An effect size of 0.2–0.4 was considered small; between 0.5–0.7, medium; and ≥ 0.8 , large.²⁷

Student's paired t -tests, with a Bonferroni correction for multiple comparisons, were used to detect for differences in the intensity of menstrual pain, as assessed by the VAS, in the morning (before administration of placebo or diclofenac potassium), and after administration of placebo or diclofenac potassium (before going to bed, during the night, and the following morning).

RESULTS

Subjective Assessment of Pain and Mood

The women's intensity of dysmenorrheic pain, as assessed by the VAS before treatment with either diclofenac potassium or placebo on the day before the overnight recordings was not significantly different between the 2 pain trials (paired t -test: $t_9 = 0.73$, $P = 0.5$; VAS rating: Pain/Placebo 72 ± 16 mm and Pain/Diclofenac 75 ± 16 mm). However, before going to bed, intensity of menstrual pain, as assessed by the VAS, was significantly lower after administration of diclofenac potassium (12 ± 25 mm) than placebo (43 ± 32 mm) (paired t -test: $t_9 = 3.51$, $P = 0.007$, effect size = -1.4). Similarly, the intensity of menstrual pain recalled by the women during the night (paired t -test: $t_9 = 3.92$, $P = 0.01$; VAS rating: Pain/Placebo 45 ± 32 mm and Pain/Diclofenac 3 ± 7 mm, effect size = -1.9) and pain intensity assessed in the morning (paired t -test: $t_9 = 3.92$, $P = 0.01$; VAS rating: Pain/Placebo 25 ± 26 mm and Pain/Diclofenac 2 ± 5 mm, effect size = -1.5) was significantly less after administration of diclofenac potassium than placebo.

There was a significant difference in the total POMS scores for the 3 trials ($F_{2,18} = 7.48$, $P = 0.004$). When the women were experiencing menstrual pain and receiving placebo, their total POMS score (133 ± 35) was significantly higher, reflecting a

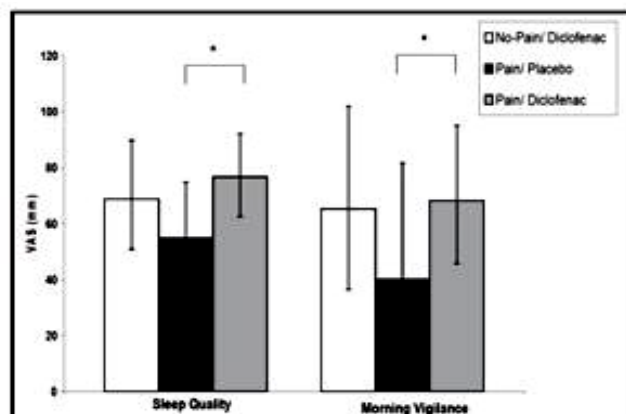


Figure 1—Sleep quality and morning vigilance as measured by the visual analogue scale (VAS, back-transformed data) in 10 women with primary dysmenorrhea when treated with either diclofenac potassium (Pain/Diclofenac) or placebo (Pain/Placebo) during menstruation, and when treated with diclofenac potassium during a pain-free phase of the menstrual cycle (mid-follicular, No-Pain/Diclofenac). * $P < 0.05$ (RM-ANOVA with a Tukey post hoc test).

poorer mood, compared to when they were in the pain-free phase of the menstrual cycle (102 ± 17) ($P < 0.01$; Tukey post-test). Administration of diclofenac potassium for menstrual pain, compared to placebo, tended to decrease total POMS scores (112 ± 28), although not significantly ($P > 0.05$). The effect size for the POMS score reduction was -0.6 .

Subjective Assessment of Sleep Quality and Morning Vigilance

Figure 1 shows the women's sleep quality and morning vigilance, as measured by the VAS, when they were not experiencing menstrual pain (No-pain/Diclofenac) and when they were experiencing menstrual pain and receiving either diclofenac (Pain/Diclofenac) or placebo (Pain/Placebo). Analysis of variance showed that there were significant differences in sleep quality ($F_{2,18} = 5.56$, $P = 0.01$) and morning vigilance ($F_{2,18} = 3.77$, $P = 0.04$) across the 3 trials. When the women were experiencing menstrual pain and receiving placebo (Pain/Placebo), they tended to rate their sleep quality as poorer, although not significantly in post hoc analysis, compared with the pain-free phase of the menstrual cycle (56 ± 19 mm vs. 70 ± 20 mm). Similarly, the women tended, although not significantly, to rate their morning vigilance as poorer after receiving placebo for their menstrual pain compared with the pain-free phase of the menstrual cycle (47 ± 26 mm vs. 69 ± 27 mm). Administration of diclofenac potassium for menstrual pain, compared to placebo, significantly improved their sleep quality (77 ± 15 mm, $P < 0.05$; Tukey post-test, effect size = 1.3) and morning vigilance (70 ± 23 mm, $P < 0.05$; Tukey post-test, effect size = 0.9) to values not significantly different to those measured in the pain-free phase of the menstrual cycle (Figure 1).

Polysomnographic (PSG) Sleep Variables

The women's PSG variables for the 3 trials are shown in Table 2. TIB, TST, SOL, wake during sleep, latency to REM

Table 2—Polysomnographic (PSG) Sleep Variables Assessed During the 3 Overnight Trials in 10 Women with Primary Dysmenorrhea when Treated with Either Diclofenac or Placebo During Menstruation (Pain/Diclofenac and Pain/Placebo) or During the Mid-Follicular Phase when the Women were Pain-Free (No-Pain/Diclofenac)

Polysomnographic data	No Pain/Diclofenac	Pain/Placebo	Pain/ Diclofenac
Time in bed (min)	464 ± 54	443 ± 31	439 ± 76
Total sleep time (TST) (min)	450 ± 54	420 ± 33	425 ± 76
Sleep onset (min)	10 ± 9	16 ± 10	9 ± 6
Sleep efficiency (%)	97 ± 1	95 ± 3*	97 ± 1
Wake during sleep (min)	9 ± 6	12 ± 6	8 ± 4
Stage 1 (%TST)	4 ± 2	6 ± 3**	4 ± 1
Stage 2 (%TST)	53 ± 8	58 ± 7	54 ± 6
SWS (%TST)	17 ± 6	14 ± 5	16 ± 5
REM (%TST)	26 ± 4	22 ± 5**	26 ± 3
Latency to stage 3 (min)	11 ± 3	13 ± 5	12 ± 3
Latency to REM (min)	76 ± 14	74 ± 27	67 ± 9
Stage changes (per hour sleep)	15 ± 2	18 ± 2†	14 ± 2

Values are expressed as mean ± SD. *P < 0.05, **P < 0.01 between No-Pain/Diclofenac and Pain/Placebo. †P < 0.05, ‡P < 0.01 between Pain/Placebo and Pain/Diclofenac.

sleep, % stage 2 sleep, and % SWS did not differ significantly between any of the recording nights for the women. However, there were significant effects for sleep efficiency ($F_{2,18} = 7.04$, $P = 0.006$), % stage 1 sleep ($F_{2,18} = 7.40$, $P = 0.005$), % REM sleep ($F_{2,18} = 6.84$, $P = 0.006$), and number of stage changes per hour ($F_{2,18} = 5.13$, $P = 0.02$).

During the Pain/Placebo trial compared to the No-Pain/Diclofenac trial, the women had reduced sleep efficiency ($P < 0.05$; Tukey post-test), less % REM sleep ($P < 0.05$; Tukey post-test), and more % stage 1 sleep ($P < 0.01$; Tukey post-test). Administration of diclofenac potassium for menstrual pain reversed the effects of pain on sleep. Compared to placebo, the women had a better sleep efficiency ($P < 0.05$; Tukey post-test, effect size = 1.0), more % REM sleep ($P < 0.01$; Tukey post-test, effect size = 1.1), less % stage 1 sleep ($P < 0.05$; Tukey post-test, effect size = -0.9), and a significant decrease in the number of stage changes per hour of sleep ($P < 0.05$, effect size = -1.7). Therefore, diclofenac potassium administered for menstrual pain restored these sleep variables to values not significantly different to those measured in the pain-free phase of the menstrual cycle (Table 2).

DISCUSSION

To our knowledge, this is the first study that demonstrates that the NSAID diclofenac potassium effectively treats daytime and nighttime dysmenorrheic pain and is associated with an improvement in subjective and objective measures of sleep quality. When the women were experiencing menstrual pain and did not receive pain relief with placebo, they had reduced sleep efficiency, less REM sleep, and more stage 1 sleep during the night compared with a pain-free phase of the menstrual cycle. A recommended daily dose of diclofenac potassium (150 mg), when taken as 50 mg capsules twice during the day and once before bedtime, compared to placebo, attenuated the women's menstrual pain and was associated with improved ratings of sleep quality and morning vigilance. Also, when dysmenorrheic pain was treated with diclofenac potassium, the women's sleep

architecture was restored to a level recorded when the women were in a pain-free phase of the menstrual cycle.

A previous investigation by our group found that women with dysmenorrhea reported significantly poorer subjective sleep quality during menstruation compared to when they were in pain-free phases of the menstrual cycle, and compared to a group of women without dysmenorrhea.⁷ Although not significant, the results of this study show a similar tendency for poorer subjective sleep quality in women experiencing dysmenorrheic pain compared with a pain-free phase of the menstrual cycle. Similarly, patients with chronic pain frequently report disturbed and "unrefreshing" sleep.²⁸ Analysis of sleep architecture in the women in our study also indicated disturbed sleep in association with dysmenorrheic pain. The women had a significantly lower SE, less REM sleep, and more stage 1 sleep when they were experiencing menstrual pain and receiving placebo, compared to when they were in a pain-free phase of the menstrual cycle. The reduction in sleep efficiency was probably due to a combination of nonsignificant increases in SOL and in-bed wakefulness (Table 2). These findings support those of Baker et al.,⁷ although the extent of sleep disturbance in association with dysmenorrheic pain was less in this study, possibly due to lower pain intensity before bed (on average, 43 mm) compared with the previous study (on average, 81 mm).⁷ There may have been a placebo effect in this study; in studies of antinociception in which subjects have an expectation of pain relief, placebos invariably are effective, at least in some patients, irrespective of the etiology of the pain.²⁹ Indeed, previous investigations of efficacy of pharmaceutical management of dysmenorrheic pain have reported that 15% to 33% of patients with primary dysmenorrhea responded favorably to placebo administration.³⁰ In addition, rescue medications were used during the day by several subjects, which may have reduced their nighttime pain severity. It is therefore likely that in the absence of any medication, women with dysmenorrhea may experience significantly greater sleep disturbances than suggested from this study.

Our finding of increased stage 1 sleep in association with dysmenorrhea is similar to findings of Baker et al.⁷ and to find-

ings in patients with chronic pain. Drewes et al. reported an increase in stage 1 sleep in subjects with rheumatoid arthritis.³¹ Similarly, a study of osteoarthritic patients revealed that they had a greater percentage of stage 1 sleep compared with age- and sex-matched healthy controls.³² Stage 1 sleep is considered a transitional sleep stage,³³ and increased stage 1 sleep is associated with the perception of unrefreshing sleep and poor sleep quality.^{34,35}

The efficacy of diclofenac potassium and other NSAIDs such as ibuprofen, naproxen, rofecoxib, and valdecoxib, in alleviating menstrual pain, has been documented.^{19,46,47} In our study, administration of diclofenac potassium, taken as three 50 mg doses alleviated the women's dysmenorrhea during the day and night. The women's menstrual pain intensity, as assessed by the 100-mm VAS, was reduced from 75 ± 16 mm before administration of diclofenac potassium in the morning to values of 12 ± 25 mm before going to bed, 3 ± 7 mm during the night, and 2 ± 5 mm the following morning; significantly lower than after placebo at all time points. Our study is the first to show that diclofenac potassium is effective in attenuating nighttime menstrual pain and restoring objective and subjective measures of sleep to values measured when the women were in a pain-free phase of the menstrual cycle. Administration of diclofenac potassium compared to placebo, not only attenuated the women's menstrual pain, but also increased sleep efficiency and amount of REM sleep and decreased the amount of stage 1 sleep during the night, with large effect sizes. Diclofenac potassium also decreased the number of sleep stage changes per hour of sleep, indicating a less fragmentary sleep. Finally, diclofenac potassium improved the women's subjective ratings of sleep quality and morning vigilance. Our results support the use of diclofenac potassium in treating dysmenorrheic pain to restore sleep quality in women during menstruation.

Investigations on the effect of pain medications on sleep in patients with other pain-related disorders, is limited. To our knowledge, only one study to date, has examined the effects on subjective and objective measures of sleep of administration of an NSAID in patients with pain.³⁶ In that study, a daily dose of 20 mg of the NSAID tenoxicam, was administered to 13 patients with rheumatoid arthritis over a 90-day period.³⁶ Although subjective sleep quality was improved, tenoxicam had no effect on any of the measured objective sleep parameters.³⁶ The presence of other factors such as concomitant depression, altered mood states, poor physical condition and anxiety, can influence the relationship between sleep and pain,³⁷ and may explain the poor effectiveness of pain medications in restoring sleep architecture in patients with some pain-related disorders, such as rheumatoid arthritis.³⁶ In addition, young adult subjects typically have better sleep compared with older subjects.³³ Therefore, age may also account for the different outcomes between the effect of NSAID administration on sleep architecture in the women in our study (21 ± 1 years) and the patients with rheumatoid arthritis (59 ± 11 years) in the study by Lavie et al.³⁶

A secondary finding of our study was that women had poorer moods when they were experiencing menstrual pain and receiving placebo than when they were in a pain-free phase of the menstrual cycle; this is consistent with a growing body of literature that suggests a compelling and consistent relationship exists between pain and mood.^{13,38,39} For example, a positive

and significant relationship between pain and mood has been demonstrated in both adults and children suffering from arthritis.^{40,41} Administration of diclofenac potassium during painful menstruation tended to improve the women's mood, with a moderate effect size, by returning mood scores closer to those scored during the pain-free phase of their menstrual cycle.

There are limitations to our study that need to be considered. We recruited ten women who successfully fulfilled all the criteria for participation in the study, and who were prepared to participate in a lengthy study protocol. The sample size was sufficient to detect differences in sleep quality, mood, and in the sleep PSG, when women were suffering from dysmenorrheic pain unrelieved by placebo. However, nonsignificant trends that we found may have been significant if a larger sample had been used. Further, changes in EEG recordings can be subtle and not easily detectable when scoring sleep records according to standard criteria.²⁵ Studies on sleep in patients with other painful syndromes, such as rheumatoid arthritis, have found changes in the sleep EEG such as increased α activity, which is thought to contribute to the poor subjective sleep quality experienced by these patients.³¹ More advanced measures, such as EEG power spectral analyses, may identify pain-related microarousals or changes in the EEG spectrum during the night in women with dysmenorrhea. Despite the small sample size and lack of sophisticated sleep scoring measures, we were still able to detect PSG disruptions in sleep that were sufficient to make conclusive deductions that menstrual pain negatively affects sleep and that diclofenac potassium is able to restore subjective and objective measures of sleep.

We assessed the women's subjective nighttime pain when they woke up in the morning by asking them to recall the pain they experienced during the night. The method of retrospective pain scoring is one of considerable controversy. While some researchers believe that pain experiences can be recalled accurately,⁴⁸⁻⁵¹ others claim that reports of retrospective pain are inaccurate and therefore unreliable; patients have often been found to overestimate their pain when asked to recall its intensity,⁵²⁻⁵⁴ however, cases of retrospective underestimation of pain have also been reported.⁵⁵ These conflicting findings have been attributed to several factors, including the patient's mood⁵⁶ and pain intensity at the time of recall.^{54,57} It is, therefore, possible that the women's rating of nighttime menstrual pain was influenced by the perceived pain intensity experienced during the time of recall in the morning.

Ethically, the women were free to take rescue medication, or medication which they would normally take, if they felt that the administered capsule did not provide adequate pain relief. Several women did take rescue medication during their Pain/Placebo trial, and by doing so created a limitation in the study. Nevertheless, although six of the ten women took rescue medication during the placebo arm of the pain trial, the intensity of their menstrual pain before bed was still significantly greater, and their sleep was more disturbed, compared to when they had taken diclofenac potassium. However, more substantial disturbances in sleep architecture due to pain may have been masked by the rescue medication.

Primary dysmenorrhea is the most common gynecological disorder experienced by women of child-bearing age,^{42,43} and results in a high degree of school and work absenteeism.⁵ There-

fore, the ability of diclofenac potassium to restore pain-reduced subjective measures of sleep quality and morning vigilance, as well as objective measures of sleep architecture to their pain-free state is extremely important and relevant in improving the quality of life of women with primary dysmenorrhea. It has been well established that COX inhibitors cause GI side effects such as gastric ulceration.^{4,16-18,44} However, GI side effects are usually associated with chronic administration in older patients⁴⁴ and are generally of less concern in acute administration of the drug (as would occur in the treatment of primary dysmenorrhea).⁴⁵ In this study, administration of diclofenac potassium was well tolerated and did not cause any adverse effects. Therefore, diclofenac potassium appears to be a safe and effective option for the treatment of dysmenorrhoeic pain.

In conclusion, we have shown that compared to placebo, 150 mg of diclofenac potassium, given as two doses of 50 mg during the day and as a 50 mg dose in the evening before bedtime, is effective in attenuating menstrual pain and in restoring both objective and subjective sleep quality to levels measured when women with primary dysmenorrhea were in a pain-free phase of the menstrual cycle.

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CHAPTER SIX

CONCLUSION

CONCLUSION

The visible sign marking the start of the menstrual cycle is the cardinal event of menstrual bleeding, or menstruation. In some women with normal ovulatory menstrual cycles, menstruation is pain-free, or only mildly painful or discomforting. However, in 45-95% of otherwise healthy women with normal ovulatory menstrual cycles, menstruation is more painful, and in approximately 10-25% of these women the intensity of the menstrual pain, or dysmenorrhoea, is very severe (Andersch and Milsom 1982; Sundell *et al.* 1990; Hofmeyr 1996; Proctor and Farquhar 2006; Unsal *et al.* 2010; Grandi *et al.* 2012). In these women, primary dysmenorrhoeic pain begins shortly after menarche and persists in association with most menstrual periods throughout their reproductive lives. Despite the far-reaching negative impact that painful menstruation may have on women's lives and health, dysmenorrhoea remains a poorly understood disorder that many women simply accept as a normal part of their menstrual cycle (Reddish 2006). The research presented in this thesis has addressed several gaps in the literature about the impact and treatment of primary dysmenorrhoea.

As part of the work described in this thesis, I aimed to determine whether women with severe primary dysmenorrhoea have an altered sensitivity to pain compared to non-dysmenorrhoeic women, considering menstrual cycle phase, referred and non-referred areas of pain, and different experimental pain modalities. My findings demonstrate that compared to women without dysmenorrhoea, women who experience monthly severe primary dysmenorrhoeic pain are hyperalgesic to two different clinically-relevant forms of experimentally-induced deep-muscle pain, namely, ischaemia and injection of the algescic substance, hypertonic saline. My findings are consistent with the only other study in which deep-muscle pain was induced, in this case with electrical stimulation, in women with and without dysmenorrhoea (Giamberardino *et al.* 1997). As

discussed in the Introduction of this thesis, the conflicting results in the literature regarding whether sensitivity to painful stimuli differs between women with and without dysmenorrhoea have been attributed to methodological differences in study design. Indeed, a diverse range of stimulations have been applied to various body locations, and at varying tissue depths. Given that the extent of hyperalgesia is different in the skin compared to subcutaneous tissue and compared to deep muscle tissue (Vecchiet *et al.* 1990; Giamberardino *et al.* 1993; Giamberardino *et al.* 1997), and that the structures that become hyperalgesic under recurrent visceral pain conditions such as dysmenorrhoea, are primarily the muscles (Vecchiet *et al.* 1990; Giamberardino *et al.* 1993), I believe that my results are compelling, especially since my study design accounts for many of the methodological concerns of previous research in this field.

My findings also showed that the muscle hyperalgesia in women with primary dysmenorrhoea was present when they were experiencing menstrual pain as well as during non-painful phases of the menstrual cycle, and was present in muscles within and outside the area of referred menstrual pain. These findings are important because they show that differences in pain sensitivity in these women are not tied purely to menstruation and are wide-spread in muscle tissue. My findings support the proposed hypothesis that women with dysmenorrhoea are sensitised to deep-muscle pain, which may be due to a combination of impaired pain inhibition and amplified pain facilitation (Tu *et al.* 2010) mediated by functional and structural changes within the CNS (Tu *et al.* 2009; Tu *et al.* 2010; Vincent *et al.* 2011). Increased sensitivity to experimental pain is believed to be a risk factor for developing chronic pain (Carli *et al.* 2002; Staud *et al.* 2003). However, without a longitudinal study in dysmenorrhoeic women it is not possible to discern whether the increased sensitivity to muscle pain is the cause or the effect of recurrent menstrual

pain. Given that genetic factors have been shown to have a significant aetiological contribution to both chronic pain conditions (Kato *et al.* 2006), and experimentally-induced pain (Norbury *et al.* 2007; Williams *et al.* 2012), it would be valuable for future studies to investigate pain sensitivity in female adolescents with primary dysmenorrhoea soon after menarche or in female adolescents at high risk for developing dysmenorrhoea to help determine whether they have an underlying sensitivity to pain. Regardless of cause and effect, however, the growing evidence of altered pain perception in women with primary dysmenorrhoea implies that it is essential to limit the cyclic noxious input into the CNS by effectively treating dysmenorrhoeic pain; such treatment may potentially reduce the likelihood of developing hyperalgesia, or central sensitivity to pain.

The importance of restricting the repeated noxious input, by effective analgesic treatment, is further highlighted by reports that 1) the morphological brain changes seen in women with dysmenorrhoea are similar to those seen in patients with chronic painful conditions (Davis *et al.* 2008; Blankstein *et al.* 2010; As-Sanie *et al.* 2012), 2) dysmenorrhoea is a frequent co-morbid symptom in women with chronic pelvic pain, and 3) dysmenorrhoea has recently been proposed to predispose women to other chronic painful conditions (As-Sanie *et al.* 2012). What is promising, nevertheless, is that longitudinal studies suggest that the central changes in chronic pain states are dynamic, and therefore reversible after removal of the nociceptive source (Teutsch *et al.* 2008; Gwilym *et al.* 2010), although such investigations have not yet been conducted in women with dysmenorrhoea. Future studies should investigate whether the central and behavioural changes to painful stimuli in women with dysmenorrhoea are still present after a period of effective treatment of menstrual pain.

Since my studies about pain sensitisation included women with and without primary dysmenorrhoea studied at two or three phases of confirmed ovulatory menstrual cycles, I was also able to address the question of whether menstrual cycle phase impacts pain sensitivity. My results confirmed those of other recent, well-controlled studies showing that menstrual cycle phase has no effect on the perception of pain in women with (Granot *et al.* 2001; Vincent *et al.* 2011) and without (Granot *et al.* 2001; Bajaj *et al.* 2002; Straneva *et al.* 2002; Sherman *et al.* 2005; de Leeuw *et al.* 2006; Kowalczyk *et al.* 2006; Klatzkin *et al.* 2010; Rhudy and Bartley 2010; Vincent *et al.* 2011) dysmenorrhoea. The lack of effect of menstrual cycle phase on pain sensitivity may be surprising, considering the dramatic fluctuations in reproductive hormones across the cycle and that studies in animals have shown that progesterone and oestradiol influence the pain response (Maggi *et al.* 1989; Fillingim and Ness 2000; Craft *et al.* 2004). However, there is a complex interaction of reproductive hormones at each menstrual phase and the lack of change in pain sensitivity across the menstrual cycle may be a consequence of the combined effect of pronociceptive and antinociceptive actions of oestrogen and progesterone (Craft *et al.* 2004; Deroo and Korach 2006; Stening *et al.* 2007; Martin 2009). Also, as suggested in a recent review (Craft 2007), oestrogen may affect some but not all forms of pain. For example, the decline in gonadal hormones at the end of the luteal phase is associated with a greater incidence of migraines, temporomandibular and back pain (Kuba and Quinones-Jenab 2005). The interaction between the gonadal hormones and pain perception is intricate and not entirely understood. Hormonal effects on nociceptive processing likely are the result of actions at multiple levels, from the peripheral nerve to the highest cortical response and may be pronociceptive or antinociceptive in nature, depending on the hormonal profile, as well as the sum of their pronociceptive and antinociceptive effects (Craft *et al.* 2004; Deroo and Korach

2006; Martin 2009). Possibly, further studies of women taking hormonal treatments of a progestin alone or progestin and oestradiol in combination (such as oral contraceptives) may be able to more directly address the question of how these female reproductive hormones impact pain sensitivity.

Taken together, my studies in women with and without primary dysmenorrhoea have advanced our understanding about the impact of both menstrual cycle phase and the presence of severe menstrual pain on pain sensitivity.

The painful menstrual cramps experienced by women with dysmenorrhoea may be considerably disabling and are a primary cause of recurrent short-term school or work absenteeism among young women of child-bearing age (Sundell *et al.* 1990; Coco 1999). As part of my studies, I assessed quality of life and mood in women with primary dysmenorrhoea. I found that women with severe primary dysmenorrhoea experienced significantly poorer moods (Chapter 2 and Chapter 5) and a poorer quality of life (Chapter 3) when experiencing menstrual pain compared to pain-free phases of the menstrual cycle, and compared to pain-free healthy control women.

In various large cross-sectional studies conducted worldwide involving hundreds-to-thousands of women and/or female adolescents, menstrual pain has been reported to have a negative impact on multiple aspects of the personal lives of those affected, including: family relationships, friendships, school/work performance, and social and recreational activities (Ortiz *et al.* 2009; Eryilmaz *et al.* 2010; Wong and Khoo 2010; Pitangui *et al.* 2013). Although

these studies did not assess quality of life, *per se*, the aspects of these women's lives reported to be impacted by their dysmenorrhoeic pain are all components included in the assessment of quality of life. My findings extend this epidemiological research to show that women with severe primary dysmenorrhoea experience a poorer health-related quality of life during menstruation. During a phase outside of menstruation, however, quality of life was similar in women with and without dysmenorrhoea, providing evidence of a strong link between pain and a poor quality of life. However, to confirm this link between poor quality of life and pain, future studies should extend my study by assessing quality of life during the non-painful luteal phase too. Health-related quality of life has been reported to be impaired in patients with pain (Langley 2012), particularly chronic pain (Laursen *et al.* 2005; O'Connor 2009). There are, however, limited studies investigating the relationship between recurrent pain and quality of life. To my knowledge, quality of life has been explored in one other recurrent pain condition (Matusiak *et al.* 2010). In this study, the quality of life scores ($56 \pm 15\%$) of patients with hidradenitis suppurativa, a recurrent painful dermatological condition, are comparable to those scored by women experiencing primary dysmenorrhoeic pain ($54 \pm 18\%$) in my study. Furthermore, I found that menstrual pain interferes with multiple domains of quality of life; a finding in agreement with studies investigating quality of life in patients with chronic neuropathic pain (O'Connor 2009), and pain due to fibromyalgia/whiplash (Laursen *et al.* 2005). Given the significant impact of dysmenorrhoeic pain on quality of life, primary dysmenorrhoea should not be accepted by women as an unavoidable disorder linked to menstruation and they should be encouraged to seek treatment.

Not only is personal quality of life impacted by dysmenorrhoeic pain, there is also substantial costs to society. Dysmenorrhoea is a common cause of recurrent short-term school or work absenteeism in young women (Andersch and Milsom 1982; Sundell *et al.* 1990; Ortiz *et al.* 2009; Wong and Khoo 2010; Pitangui *et al.* 2013), with an estimated 10-30% of all working or studying women with dysmenorrhoea losing 1-2 working days per month. This amounts to an annual loss of approximately 600 million working hours or up to \$2 billion annually in the United States (Dawood 1988). In a Swedish population of only 4 million, primary dysmenorrhoea has been reported as the cause of 230 000 lost working days, with more than 50% of women claiming absenteeism from work or school on at least one occasion due to dysmenorrhoea. Thus, given the significant impact of dysmenorrhoea on productivity, it ultimately can have severe worldwide economic consequences (Hofmeyr 1996; Jones 2004). Given that most women do not seek medical attention for their pain, and that most cases go undocumented because many women still believe that menstrual pain is a normal part of the female menstrual cycle (Ortiz *et al.* 2009; Ortiz 2010; Wong 2010; Wong and Khoo 2010), these numbers may even be underestimates.

Mood was included as a single item in the quality of life measure. Women with dysmenorrhoea had a median score of 2 (out of 5) compared to a median score of 4 in non-dysmenorrhoeic women during menstruation and 4 in their own pain-free follicular phase, reflecting that mood was likely impacted by the pain. I also assessed mood more thoroughly using the profile of mood states (POMS) questionnaire, a validated scale of current mood. I found that women with dysmenorrhoea had a poorer mood when they were experiencing menstrual pain compared to a pain-free menstrual phase and compared to women without dysmenorrhoea (Chapter 2a). This

may not be surprising given that mood, or psychological distress, is intimately related to pain. Importantly, the relationship is bidirectional, such that pain exacerbates psychological distress, and psychological distress exacerbates pain (Von Korff and Simon 1996; Bair *et al.* 2003). The emotional response to pain is coupled with autonomic, endocrine, and immune responses which may amplify pain through psychophysiological pathways (Garland 2012). Negative emotions are also associated with increased activation in the amygdala, anterior insula, and anterior cingulate cortex (ACC), structures that mediate the processing of emotions and which turn attention towards pain, thereby intensifying pain unpleasantness (Garland 2012). Pain unpleasantness often is, though not always, related to pain intensity (Price 2000), and the relationship between pain unpleasantness and feelings of anxiety, depression and fear of pain is particularly evident in patients with chronic pain (Wade *et al.* 1990; Wade *et al.* 1996). Further, pain-related fear has been shown to be more disabling than the pain itself in chronic pain patients (Crombez *et al.* 1999). A noteworthy distinction must however, be made between the negative emotional-affective components of clinical pain compared with that of experimental pain. Although anticipation of experimental pain may cause some anxiety, its emotional component is distinct from that of clinical pain. For example, the amygdala is activated during chronic arthritic pain, but not during acute experimental pain (Kulkarni *et al.* 2007). In addition, affective VAS ratings of unpleasantness have been reported to be significantly higher in patients experiencing various forms of clinical pain compared to experimentally-induced pain (Price *et al.* 1987). That said, it is also true that experimental pain can be modulated by pain-related emotions (Rainville *et al.* 2005), and induced negative mood (Loggia *et al.* 2008).

There is limited evidence that female reproductive hormones may modulate the emotional response to pain; one study used whole-brain fMRI to investigate functional brain responses to painful heat stimuli in healthy women across the menstrual cycle. Although behavioural pain thresholds did not differ between menstrual cycle phases, differences were found in the magnitude of activation of the ACC upon painful heat stimulation between periods of low and high oestrogen concentrations (de Leeuw *et al.* 2006). Given that the ACC has been implicated in the emotional processing and anticipation of pain (Ploghaus *et al.* 1999; Peyron *et al.* 2000; Beckmann *et al.* 2009), the authors concluded that the emotional-affective component of pain may be enhanced during periods of low oestrogen (de Leeuw *et al.* 2006), which supports both human and animal studies suggesting that oestrogen has anti-anxiety effects (McEwen and Alves 1999). These findings also suggest that although a behavioural response to an experimental pain stimulus may not change, there may still be different activation patterns in the brain to painful stimuli in association with fluctuating reproductive hormone levels at different phases of the menstrual cycle. It is also interesting to speculate that the impact of dysmenorrhoeic pain on mood may be enhanced compared to other types of pain in women because dysmenorrhoea occurs during the low-oestrogen early follicular phase of the menstrual cycle.

A major aim of my thesis was to investigate night-time dysmenorrhoeic pain. Almost all the studies that have investigated dysmenorrhoea have focused on the impact of menstrual pain on day-time functioning and treatment of the pain. To date, as far as I am aware, only two other studies have investigated the impact of dysmenorrhoeic pain on subjective and objective measures of sleep. In my study described in Chapter 5, I showed the negative effects of severe primary dysmenorrhoeic pain on subjective measures of sleep quality and objective measures of sleep

architecture. My findings substantiate one of the two previously published studies on objective sleep disturbances in women with primary dysmenorrhoea, which found that severe dysmenorrhoeic pain was associated with PSG sleep disturbances, including reduced sleep efficiency and extended time spent awake, moving and in light Stage 1 sleep, compared to two pain-free phases of the menstrual cycle, and with controls (Baker *et al.* 1999a). The other, less-controlled study, found no differences in the PSG recordings of women with and without menstrual pain (Araujo *et al.* 2011). However, they included older women with less severe primary or secondary dysmenorrhoeic pain, to which sleep may have been resilient.

My findings of subjective and objective sleep disturbances due to dysmenorrhoeic pain, supports the existence of an intricate relationship between pain and sleep. Pain is believed to be the primary cause of insomnia in patients with various medical conditions (Drewes and Arendt-Nielsen 2001), and there is evidence showing that pain is associated with poorer subjective (Moffitt *et al.* 1991; Lavigne *et al.* 2005; Kelly *et al.* 2012; Nicassio *et al.* 2012) and objective (Jennum *et al.* 1993; Drewes *et al.* 1998; Drewes and Arendt-Nielsen 2001; Onen *et al.* 2005; Blagestad *et al.* 2012) measures of sleep. Most studies investigating sleep and pain have been conducted in patients with long-term chronic pain such as fibromyalgia and rheumatoid arthritis (Drewes 1999; Lavigne *et al.* 2005; Wolfe *et al.* 2006). These conditions are complicated by a diverse symptomatology, including stiffness and widespread pain. Studying sleep in women with cyclical dysmenorrhoeic pain provides the unique opportunity to study participants in the presence and absence of an acute, severe pain. My findings that women with primary dysmenorrhoea have disrupted sleep only during menstruation – a time when they report severe night-time pain – provides compelling evidence that pain is the cause of their

sleep disturbance. While other factors associated with menstruation, such as heavy blood flow, could conceivably also disrupt sleep, it is likely that these factors would be common to controls too, and they did not experience disturbed sleep during menstruation. However, to confirm this link between poor sleep quality and pain, future studies should extend my study by the sleep of women with dysmenorrhoea during the non-painful luteal phase too.

Importantly, although understanding of the mechanism underlying the interactive relationship between pain and sleep is still evolving (Onen *et al.* 2001), there is a growing body of data suggesting a reciprocal nature of this relationship, such that pain disrupts sleep and disturbances in sleep modify pain perception (Onen *et al.* 2001; Ohayon 2006). In the context of dysmenorrhoea, preliminary findings show that young women with insomnia experience more severe menstrual pain compared with young women who do not have insomnia (Woosley and Lichstein 2013). It is possible, therefore, that disturbed sleep as we found in women with severe primary dysmenorrhoea during menstruation, may heighten their sensitivity to pain. Indeed, a recent study of a population of chronic pain patients found that actigraphy-based measures of sleep, particularly total sleep time and wake after sleep onset, predicted pain severity the following day (Tang *et al.* 2012). However, contrary to our findings, the same study found that pre-sleep pain did not predict subsequent sleep (Tang *et al.* 2012). The different study populations may account for the contrasting results; I used young, otherwise healthy women with primary dysmenorrhoea with no sleep disorders, while Tang *et al.*, (2012) used predominantly middle-aged women with both chronic pain and insomnia.

From the current literature, it is clear that the sleep-pain relationship is complex and one that is challenging and difficult to unravel. Study sample characteristics, meticulous assessment of sleep, nociceptive stimuli, and individual differences in pain perception are all factors that need to be carefully considered before we can delineate this multifaceted relationship. To add to this complexity, recent studies have suggested that negative mood may be a mediator between sleep and chronic pain, such that poor sleep leads to a worse mood, which leads to greater pain intensity (O'Brien *et al.* 2010). In my studies, I investigated all three of these variables (sleep, mood, and pain intensity). While I found that women with primary dysmenorrhoea had severe pain, poor sleep quality and poor mood during menstruation, my study was not designed or sufficiently powered to examine the directionality of relationships between these factors. Clearly, investigation of mediating factors in the relationship between pain and sleep is an emerging important future direction for pain research. In my opinion, primary dysmenorrhoea is a useful and good model to investigate the relationship between pain, sleep and mood, as not only is it recurring with a predictable onset, but it allows for sleep investigations during natural pain conditions and natural pain-free conditions.

On account of the prostaglandin-based aetiology of primary dysmenorrhoeic pain, the current most common pharmacological treatment for dysmenorrhoea is NSAID use. In Chapters 4 and 5 of this thesis, my research presents further evidence that the NSAID, diclofenac potassium, provides effective analgesic relief from day-time and night-time primary dysmenorrhoeic pain. My research study in Chapter 4 aimed to assess the progression of dysmenorrhoeic pain across a 24 hour period and to investigate the efficacy of diclofenac potassium in relieving dysmenorrhoeic pain across this time period. I found that the daily recommended dose of diclofenac potassium

(150 mg) administered at three set intervals across the day provided effective and superior pain relief compared to placebo; even when including the quarter of the sample that resorted to rescue medications during the course of the assessment period.

Although my finding that diclofenac potassium is an effective treatment for day-time menstrual pain (Chapter 4) concurs with other observations, no previous study, to my knowledge, has investigated whether diclofenac potassium is effective in relieving night-time menstrual pain. As presented in Chapter 5, I report for the first time that the NSAID, diclofenac potassium, is able to provide effective relief from night-time menstrual pain and, more importantly, is able to restore both subjective and objective measures of sleep composition to those observed during a pain-free phase of the menstrual cycle. Also, evening mood tended to improve on the night of diclofenac potassium treatment compared with placebo.

Collectively, the results of my studies, and those of other researchers discussed in the Introduction of this thesis, show diclofenac to be an effective and well-tolerated pharmacological treatment for primary dysmenorrhoeic pain (Ingemanson *et al.* 1981; Riihiluoma *et al.* 1981; Frolich 1997; Warner *et al.* 1999; Letzel *et al.* 2006; Chantler *et al.* 2008). Most research on the use of diclofenac for the treatment of dysmenorrhoea has focused on diclofenac sodium. Although pharmacokinetic studies show similar bioavailability between diclofenac sodium and potassium, the mean time to reach maximal plasma levels is shorter with diclofenac potassium (± 30 minutes) (Moore 2007) compared with diclofenac sodium (± 1.5 to 2 hours) (Brogden *et al.* 1980). Such properties may account for the faster onset of action with diclofenac potassium that has been reported for postoperative dental pain (Bakshi *et al.* 1992). Even though no studies have

directly compared the time efficacy of diclofenac potassium and diclofenac sodium in alleviating primary dysmenorrhoeic pain specifically, the findings of my studies (assessing pain through the day and night) and others currently available, suggest that diclofenac potassium should be considered a safe and effective option for relief from painful menses.

Despite the high prevalence of dysmenorrhoea, affecting 45-95% of menstruating women (Proctor and Farquhar 2006; Unsal *et al.* 2010) and the small yet growing body of literature that this monthly pain has a serious debilitating, and perhaps a chronic, impact on the lives of those affected, two recent papers report on the “appalling” disregard for dysmenorrhoea in the pain community (Berkley and McAllister 2011; Berkley 2013). Surprisingly little scientific attention has been given to primary dysmenorrhoea, even with regards to available research funding (Berkley, 2013). Yet, an increasing amount of evidence is indicating that the consequences of this gynaecological condition are more extensive than previously considered. In this thesis, I have confirmed many assumed consequences of moderate-to-severe menstrual pain in the lives of women with primary dysmenorrhoea. My results show that painful menstruation is associated with poorer mood, reduced quality of life, and decreased objective and subjective measures of sleep quality. Furthermore, my results support evidence suggesting that dysmenorrhoea is not merely a disorder noticeable during the menstruation phase of the menstrual cycle, particularly with regard to pain processing and the perception of pain. I found that, compared to women without dysmenorrhoea, women who experience recurrent severe primary dysmenorrhoea are hypersensitive to deep-tissue muscle pain across the menstrual cycle in muscles both within and outside the area of referred menstrual pain. These behavioural findings complement evidence from other researchers that women with dysmenorrhoea show modifications in cerebral

metabolism and structure, and that dysmenorrhoea is a frequent co-morbid symptom in women with chronic pain conditions. It is feasible that recurrent menstrual pain not only is associated with central sensitisation, but may in fact predispose women with primary dysmenorrhoea to other chronic painful conditions. Indeed, there is evidence that previous pain predicts future pain (Hunter 2001; Katz and Seltzer 2009). Limiting the noxious input into the central nervous systems of dysmenorrhoeic women therefore seems imperative to prevent the possible development of central sensitisation, as well as any potential progression of repetitive dysmenorrhoea into other chronic pain conditions. Future studies should investigate whether long-term effective treatment of moderate-to-severe menstrual pain is able to reverse any behavioural signs of central sensitisation in women with primary dysmenorrhoea, and whether any changes in cerebral structure and metabolism, as seen using sophisticated brain imagery techniques, can be restored to normal. The research presented in my thesis further highlights that the readily available NSAID, diclofenac potassium, may be useful in this capacity, having been shown to be effective not only in relieving day-time and night-time dysmenorrhoeic pain, but also in restoring objective and subjective pain-induced sleep disturbances in women with primary dysmenorrhoea. Future studies should investigate whether treatment of menstrual pain with diclofenac potassium also improves the negative impact of this pain on quality of life.

In conclusion, I have shown that the acute painful episodes of primary dysmenorrhoea have a negative impact on the quality of life, mood and sleep quality of these women. Importantly however, although these effects are restricted to the menstruation phase, and are thus acute in nature, I have also shown that women with primary dysmenorrhoea have long-lasting, widespread alterations in their sensitivity to painful stimuli. Indeed, emerging evidence is suggesting

similarities between primary dysmenorrhoea and chronic pain conditions. By means of longitudinal studies I suggest future research be directed at determining whether recurrent severe primary dysmenorrhoeic pain does indeed lead to central sensitisation, or whether dysmenorrhoea is a precursor to other chronic pain conditions. Such research will substantiate the combined findings of this thesis, which highlight the severity and impact of severe menstrual pain on the well being of women with primary dysmenorrhoea. I also showed the effectiveness of a readily-available NSAID not only for the treatment of day- and night-time pain, but also in the reversal of pain-induced sleep disturbances. Indeed, effective treatment options will be of particular importance if the hypothesis that recurrent monthly input into the CNS of women with primary dysmenorrhoea does lead to functional and structural changes within the CNS, resulting in increased sensitivity to pain, holds true.

CHAPTER SEVEN

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REFERENCES

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CHAPTER EIGHT

APPENDIX A

UNIVERSITY OF THE WITWATERSRAND
SCHOOL OF PHYSIOLOGY
SCREENING QUESTIONNAIRE

Subject profile

Date:.....

Subject name:.....

Subject code:..... *(Not to be completed by subject)*

Date of birth:..... / / 19 Age:.....

Height:.....(m) Bodymass:.....(kg)

What is your first language?

What language did you get your education in?

Contact details

Home tel:.....

Work tel:.....

Cell no. :

E-mail:.....

Other details

1. Do you smoke? **YES / NO**
2. Have you ever been pregnant, and if so, do you have children?
.....
3. Are you generally a physically healthy person? **YES / NO**
4. Have you suffered from any recent illness (within the last three months), and if so, what was the illness?
5. Are you an emotionally and psychologically healthy person? **YES / NO**
6. Do you have an intrauterine device (IUD) fitted? **YES / NO**
7. Are you taking, or have you ever taken, any form of hormonal therapy (e.g. oral contraceptive, injected contraceptive, Diane for skin)? **YES / NO**. If yes, please give details.....
.....

Your menstrual cycle

1. When did you have your very first menstrual period? (year)(age)
2. If you have a regular menstrual cycle (ie. you never miss your period AND is it roughly the same length), what is its usual length? days
3. If you do have an irregular menstrual cycle, please estimate the maximum and minimum number of days between your menstrual periods, in a typical year:
Max: days
Min: days
4. What was the date of the first day of your last period? / / 20_
5. Usual length of menstruation (bleeding)days
6. What should be the approximate date of your next period? / /20_
7. Do you suffer from menstrual pain - on the day before menstruation?
YES / NO
- during menstruation? **YES / NO**
8. When did you start suffering from menstrual pain? (year)
9. Have you always suffered from menstrual pain since your teenage years?
YES / NO
If NO, when have you not had menstrual pain?

10. Do you suffer from any complaints, such as irritability, tearfulness or bloatedness, before or during menstruation? **YES / NO**

Please specify:

.....
.....
.....

11. Do you have any complaints, apart from pain, during menstruation e.g. irritability, back-ache etc.?

.....
.....

12. Do you ever experience pain at the same place where you experience menstrual pain during the non-bleeding phase of your monthly cycle? **YES / NO**

If yes, please specify:.....

.....
.....

13. Have you ever been diagnosed by a doctor with any of the following conditions:

- | | | |
|-----|---------------------------------|-----------------|
| (a) | pelvic inflammatory disease | YES / NO |
| (b) | endometriosis | YES / NO |
| (c) | adenomyosis | YES / NO |
| (d) | uterine polyps | YES / NO |
| (e) | ovarian cysts | YES / NO |
| (f) | cervical strictures or stenosis | YES / NO |
| (g) | pelvic congestion syndrome | YES / NO |

14. Have you been under any stress lately? Please specify.

.....
.....

Severity of your menstrual pain

1. How does your menstrual pain affect your working ability?

Unaffected Rarely affected Moderately affected Severely affected

2. How often do you take pain-killers for your menstrual pain?

Not required Rarely required Often required Always required

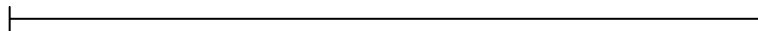
3. Do you ever suffer from nausea, headaches, diarrhoea or any other symptoms associated with your period pain?

Never Seldom Frequently Always

Explain:.....

4. Mark on the scale below how severe the pain is during menstruation.

**No pain
at all**



**Worst pain I
have ever felt**

5. At what time of the day is your period pain the worst?

Morning

Afternoon

Evening

Night

6. Body position: what happens to the pain when?

Sitting:.....

Standing:.....

Lying:.....

7. If you take medication for your menstrual pain:

What medication do you take?.....

At what dose?.....

When do you take the medication?.....

Was it prescribed by a doctor?.....

8. Is the medication effective at relieving your pain? Explain. .

.....

.
.....

9. List all the medications you have ever tried for your period pain in the past

.....

.....

.....

10. Have you ever tried taking Cataflam or Voltaren to relieve your period pain?

.....

11. If yes, was it effective?

12. Does anyone else in your family suffer from period pain? If YES,
 who?.....
13. Have you ever consulted a medical professional about your period pain?
YES/NO
 (year)

General health

1. Are you aware that you are suffering from any of the following complaints?

Diabetes	Yes	No
Hypertension	Yes	No
Muscular disorders	Yes	No
Bone disorders	Yes	No
Joint disorders	Yes	No
Gastrointestinal disorders	Yes	No
Asthma	Yes	No
Epilepsy	Yes	No
Kidney disorders	Yes	No
Liver disorders	Yes	No
Autoimmune diseases	Yes	No
Sensory disorders	Yes	No
Anxiety or Depression	Yes	No

2. Are you currently on any regular medication (i.e. that you take at least once a day)? **YES / NO**

Name of medication:.....

Taken for what?.....

Since when?.....

3. Do you take anti-inflammatories or painkillers more than once a week?

Yes

No

4. Have you ever reacted badly to anti-inflammatory medication?

Yes

No

If YES, how did you react?

.....

To what medication?

.....

5. Do you typically sleep well? **Yes** **No**

If "No", what sort of problems do you have? (tick the problem)

..... Difficulty falling asleep?

..... Waking up in the middle of the night/difficulty falling asleep again?

..... Waking up too early in the morning?

..... Disruptive leg movements/ leg discomfort?

..... Disruptive snoring/ gasping for air?

6. Do you have a regular bedtime and wake up times? **Yes** **No**

If yes; normal bedtime? :

normal wake-up time? :

Previous Pain Intensity

What is the most painful experience you have ever had?

.....

.....

People agree that the following five words represent pain in increasing intensity:

- a) Mild
- b) Discomforting
- c) Distressing
- d) Horrible
- e) Excruciating

To answer the questions below, write the letter of the most appropriate word in the space provided:

Which word best describes the worst pain you have ever

felt?.....

Which word best describes the worst toothache you have ever

had?.....

Which word best describes the worst headache you have ever

had?.....

Which word best describes the worst stomach-ache you have ever

felt?.....

Which word best describes your menstrual pain?.....

GENERAL HEALTH QUESTIONNAIRE

We should like to know if you have any medical complaints, and how your health has been in general **over the past few weeks.**

Please answer ALL the questions by simply circling the answer which you think most nearly applies to you.

Remember that we need to know about present and recent complaints, not those that you had in the past.

It is important that you try to answer ALL the questions

Thank you very much for your co-operation.

HAVE YOU RECENTLY:

1. – been able to concentrate on whatever you are doing?	Better than usual	Same as usual	Less than usual	Much less than usual
2. – lost much sleep over worry?	Not at all	No more than usual	Rather more than usual	Much more than usual
3. – been having restless, disturbed nights?	Not at all	No more than usual	Rather more than usual	Much more than usual
4. – been managing to keep yourself busy and occupied?	More so than usual	Same as usual	Rather less than usual	Much less than usual
5. – been getting out of the house as much as usual?	More so than usual	Same as usual	Less than usual	Much less than usual
6. – been managing as well as most people would in your shoes?	Better than most	About the same	Rather less well	Much less well
7. – felt on the whole you were doing things well?	Better than most	About the same	Less well than usual	Much less well
8. – been satisfied with the way you've carried out your task?	More satisfied	About same as usual	Less satisfied than usual	Much less satisfied
9. – been able to feel warmth and affection for those near to you?	Better than usual	About same as usual	Less well than usual	Much less well
10. – been finding it easy to get on with other people	Better than usual	About same as usual	Less well than usual	Much less well
11. – spent much time chatting with people	More time than usual	About same as usual	Less well than usual	Much less well
12. – felt that you are playing a useful part in things?	More so than usual	Same as usual	Less well than usual	Much less well
13. – felt capable of making decisions about things?	More so than usual	Same as usual	Less well than usual	Much less well

14. – felt constantly under strain?	Not at all	No more than usual	Rather more than usual	Much more than usual
15. – felt you couldn't overcome your difficulties?	Not at all	No more than usual	Rather more than usual	Much more than usual
16. – been finding life a struggle all the time?	Not at all	No more than usual	Rather more than usual	Much more than usual
17. – been able to enjoy your normal day-to-day activities?	More so than usual	Same as usual	Less so than usual	Much less than usual
18. – been taking things hard?	Not at all	No more than usual	Rather more than usual	Much more than usual
19. – been getting scared or panicky for no good reason?	Not at all	No more than usual	Rather more than usual	Much more than usual
20. – been able to face up to your problems?	More so than usual	Same as usual	Less able than usual	Much less able
21. – found everything getting on top of you?	Not at all	No more than usual	Rather more than usual	Much more than usual
22. – been feeling unhappy and depressed?	Not at all	No more than usual	Rather more than usual	Much more than usual
23. – been losing confidence in yourself?	Not at all	No more than usual	Rather more than usual	Much more than usual
24. – been thinking of yourself as a worthless person?	Not at all	No more than usual	Rather more than usual	Much more than usual
25. – felt that life is entirely helpless?	Not at all	No more than usual	Rather more than usual	Much more than usual
26. – been feeling hopeful about your own future?	More so than usual	About same as usual	Less so than usual	Much less hopeful
27. – been feeling reasonably happy, all things considered?	More so than usual	About same as usual	Less so than usual	Much less than usual
28. – been feeling nervous and strung-up all the time?	Not at all	No more than usual	Rather more than usual	Much more than usual
29. – felt like life isn't worth living?	Not at all	No more than usual	Rather more than usual	Much more than usual
30. – found at times you couldn't do anything because your nerves were too bad?	Not at all	No more than usual	Rather more than usual	Much more than usual

PENN DAILY SYMPTOM REPORT (DSM-IV)

DAILY SYMPTOM RATING

[illegible]

PROFILE OF MOOD STATES (POMS) QUESTIONNAIRE

NAME _____ DATE _____
SEX: Male (M) Female (F)

Below is a list of words that describe feelings people have. Please read each one carefully. Then fill in ONE circle under the answer to the right which best describes HOW YOU HAVE BEEN FEELING DURING THE PAST WEEK INCLUDING TODAY.

The numbers refer to these phrases.

- 0 = Not at all
1 = A little
2 = Moderately
3 = Quite a bit
4 = Extremely

The numbers refer to these phrases.

0 = Not at all
1 = A little
2 = Moderately
3 = Quite a bit
4 = Extremely

Col ©	O.P. ©		NOT AT ALL 1 A LITTLE 2 MODERATELY 3 QUITE A BIT 4 EXTREMELY		NOT AT ALL 1 A LITTLE 2 MODERATELY 3 QUITE A BIT 4 EXTREMELY
		21. Hopeless	0 1 2 3 4	43. Desperate	0 1 2 3 4
		22. Relaxed	0 1 2 3 4	44. Sluggish	0 1 2 3 4
		23. Unworthy	0 1 2 3 4	47. Rebellious	0 1 2 3 4
		24. Spiteful	0 1 2 3 4	48. Helpless	0 1 2 3 4
		25. Sympathetic	0 1 2 3 4	49. Weary	0 1 2 3 4
		25. Uneasy	0 1 2 3 4	50. Bewildered	0 1 2 3 4
		27. Restless	0 1 2 3 4	51. Alert	0 1 2 3 4
		28. Unable to concentrate	0 1 2 3 4	52. Deceived	0 1 2 3 4
		29. Fatigued	0 1 2 3 4	53. Furious	0 1 2 3 4
		30. Helpful	0 1 2 3 4	54. Efficient	0 1 2 3 4
		31. Annoyed	0 1 2 3 4	55. Trusting	0 1 2 3 4
		32. Discouraged	0 1 2 3 4	56. Full of pep	0 1 2 3 4
		33. Resentful	0 1 2 3 4	57. Bad-tempered	0 1 2 3 4
		34. Nervous	0 1 2 3 4	58. Worthless	0 1 2 3 4
		35. Lonely	0 1 2 3 4	59. Forgetful	0 1 2 3 4
		36. Miserable	0 1 2 3 4	60. Carefree	0 1 2 3 4
		37. Muddled	0 1 2 3 4	61. Terrified	0 1 2 3 4
		38. Cheerful	0 1 2 3 4	62. Guilty	0 1 2 3 4
		39. Bitter	0 1 2 3 4	63. Vigorous	0 1 2 3 4
		40. Exhausted	0 1 2 3 4	64. Uncertain about thing	0 1 2 3 4
		41. Anxious	0 1 2 3 4	65. Eushed	0 1 2 3 4
		42. Ready to fight	0 1 2 3 4		
		43. Good natured	0 1 2 3 4		
		44. Gloomy	0 1 2 3 4		

MAKE SURE YOU HAVE ANSWERED EVERY ITEM.

PGM 021

QUALITY OF LIFE ENJOYMENT AND SATISFACTION QUESTIONNAIRE - SHORT FORM

Q-LES-Q-SF

GENERAL ACTIVITIES

Q-LES-Q-SF

OVERALL LEVEL OF SATISFACTION

Taking everything into consideration, during the past week how satisfied have you been with your ...

	Very Poor	Poor	Fair	Good	Very Good	
... physical health?	1	2	3	4	5	(125)
... mood?	1	2	3	4	5	(126)
... work?	1	2	3	4	5	(127)
... household activities?	1	2	3	4	5	(128)
... social relationships?	1	2	3	4	5	(129)
... family relationships?	1	2	3	4	5	(130)
... leisure time activities?	1	2	3	4	5	(131)
... ability to function in daily life?	1	2	3	4	5	(132)
... sexual drive, interest and/or performance?*	1	2	3	4	5	(133)
... economic status?	1	2	3	4	5	(134)
... living/housing situation?*	1	2	3	4	5	(135)
... ability to get around physically without feeling dizzy or unsteady or falling?*	1	2	3	4	5	(136)

... your vision in terms of ability to do work or hobbies?*	1	2	3	4	5	(137)
... overall sense of well being?	1	2	3	4	5	(138)
... medication? (If not taking any, check here _____ and leave item blank) (139)	1	2	3	4	5	(140)
How would you rate your overall life satisfaction and contentment during the past week?	1	2	3	4	5	(141)

* If satisfaction is very poor, poor or fair on these items, please UNDERLINE the factor(s) associated with a lack of satisfaction.

(Under copyright)

PITTSBURGH SLEEP QUALITY INDEX QUESTIONNAIRE

PITTSBURGH SLEEP QUALITY INDEX (PSQI)

Name:..... ID No.:.....

Date:..... Age:.....

Instructions:

The following questions relate to your usual sleep habits during the past month *only*. Your answers should indicate the most accurate reply for the *majority* of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?

USUAL BED TIME _____

2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?

NUMBER OF MINUTES _____

3. During the past month, when have you usually gotten up in the morning?

USUAL GETTING UP TIME _____

4. During the past month, how many hours of *actual sleep* did you get at night? (This may be different than the number of hours you spend in bed).

HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer *all* questions.

5. During the past month, how often have you had trouble sleeping because you

- a) Cannot get to sleep within 30 minutes

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
------------------------------------	--------------------------------	-------------------------------	------------------------------------

- b) Wake up in the middle of the night or early morning

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
------------------------------------	--------------------------------	-------------------------------	------------------------------------

- c) Have to get up to use the bathroom

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
------------------------------------	--------------------------------	-------------------------------	------------------------------------

d) Cannot breathe comfortable

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
------------------------------------	--------------------------------	-------------------------------	-------------------------------------

e) Cough or snore loudly

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
------------------------------------	--------------------------------	-------------------------------	-------------------------------------

f) Feel too cold

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
------------------------------------	--------------------------------	-------------------------------	-------------------------------------

g) Feel too hot

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
------------------------------------	--------------------------------	-------------------------------	-------------------------------------

h) Had bad dreams

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
------------------------------------	--------------------------------	-------------------------------	-------------------------------------

i) Have pain

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
------------------------------------	--------------------------------	-------------------------------	-------------------------------------

j) Other reason(s), please describe:.....

.....

How often during the past month have you had trouble sleeping
because of this?

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
------------------------------------	--------------------------------	-------------------------------	-------------------------------------

6. During the past month, how would you rate your sleep quality overall?

Very good _____
Fairly good _____
Fairly bad _____
Very bad _____

7. During the past month, how often have you taken medicine (prescribed or
"over the counter") to help you sleep?

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
------------------------------------	--------------------------------	-------------------------------	-------------------------------------

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
------------------------------------	--------------------------------	-------------------------------	------------------------------------

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____
 Only a very slight problem _____
 Somewhat of a problem _____
 A very big problem _____

10. Do you have a bed partner or roommate?

No bed partner or roommate _____
 Partner/roommate in other room _____
 Partner in same room, but not same bed _____
 Partner in same bed _____

SLEEP DIARY

To be filled in first thing in the morning:

Subject code:

Date:

Study day:

1. What time did you go to bed last night? :
2. What time did you decide to go to sleep? :
3. What time did you wake up this morning? :
4. How long do you think it took you to fall asleep last night? min
5. Do you remember having a dream last night? YES / NO
6. How many times did you wake up last night?times
7. If you woke up, how long were you awake for IN TOTAL (include all awakenings)?
.....min

SLEEP QUALITY

Please make a mark on the line to indicate how well you slept last night.

No sleep |-----| Best sleep I have ever had

MORNING VIGILANCE

Please make a mark on the line to indicate how bright, fresh and alert you feel this morning.

Not at all alert and fresh |-----| Most alert and fresh I have ever felt

COMMENTS

Please make a note on whether you were disturbed during the night (medication side-effects?), were uncomfortable, or whether there was anything unusual about your sleep.

.....

.....

.....

During the course of **YESTERDAY**, did you:

1. Exercise?	Yes	No
--------------	-----	----

If yes, What exercise?.....

What time?

Duration of exercise?

2. Consume caffeine?	Yes	No
----------------------	-----	----

If yes, What caffeine? (e.g. coffee)

How much?.....

What time(s)?

3. Take a nap?	Yes	No

If yes, what time?.....

Duration of nap?

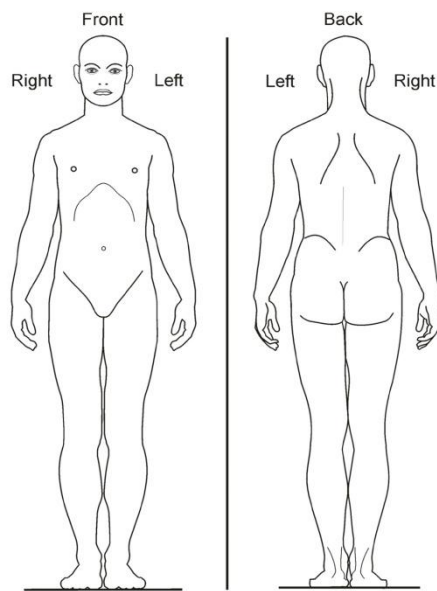
SCREENING EVENING FORM

Subject code:

Date:

Time:

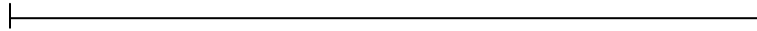
On the body chart below please indicate where you experienced pain during the day



SEVERITY OF DYSMENORRHOEA

Please make a mark on the line to indicate the degree of menstrual-associated pain you felt during the day (before taking any medication).

No pain



**Worst
pain I
have ever
felt**

Did you take any medication today, if yes:

What medication did you take?.....

What time did you take the medication?.....

How much?.....

Any other comments:

.....

.....

.....

.....

.....

SEVERITY OF DYSMENORRHOEA

Please make a mark on the line to indicate the degree of menstrual-associated pain you feel at present.

No pain |-----| **Worst pain I have ever felt**

OTHER COMMENTS

Please make a brief note of any special unpleasant features of the day, such as medication side-effects, accidents, rows, weeping, family troubles, or anything else you would like to mention:

.....
.....
.....
.....
.....
.....

SCREENING MORNING FORM

Subject code:

Date:

Study day:

1. What time did you go to bed last night? :
2. What time did you turn out the light to go to sleep? :
3. What time did you wake up this morning? :
4. How long do you think it took you to fall asleep last night? min
5. Do you remember having a dream last night? YES / NO
6. How many times did you wake up last night?times
7. If you woke up, how long were you awake for IN TOTAL (include all awakening)?
.....min

Did you have to take any medication for your menstrual-associated pain last night?

(other than the prescribed capsule given to you) If so,

What did you take?.....

What dosage?

At what time?

COMMENTS:

Please make a note on whether you were disturbed during the night, were uncomfortable, or whether there was anything unusual about your sleep. Did you experience any side-effects from the medication?

.....

.....

.....

.....

SLEEP QUALITY

Please make a mark on the line to indicate how well you slept last night.

No sleep |-----| Best sleep
I have ever
had

MORNING VIGILANCE

Please make a mark on the line to indicate how bright, fresh and alert you feel this morning.

Not at all
alert and
fresh |-----| Most alert
and fresh I
have ever
felt

SEVERITY OF DYSMENORRHOEA

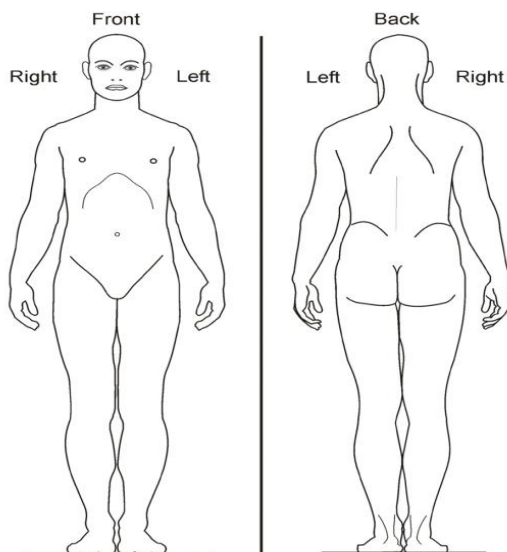
Please make a mark on the line to indicate the degree of menstrual-associated pain you feel this morning.

No pain at all |-----| **Worst pain I have ever felt**

Please make a mark on the line below to indicate the degree of menstrual-associated pain you felt during the night.

No pain |-----| **Worst pain I have ever felt**

On the body chart below please indicate where you experienced pain last night.



CHAPTER NINE

APPENDIX B

Sleep and Menstrual-Related Disorders



Sleep and Menstrual-Related Disorders

Fiona C. Baker, PhD^{a,b,*}, Lynne J. Lamarche, PhD^c,
Stella Iacovides, BS^b, Ian M. Colrain, PhD^{a,d}

- Premenstrual syndrome and premenstrual dysphoric disorder
Definitions and etiology
Sleep disturbances
Daytime sleepiness and alertness
Circadian rhythm disturbances
Sleep deprivation studies
- Primary dysmenorrhea
Definition and etiology
Sleep disturbances
- Menstrual-associated sleep disorder
- Summary
- References

Many women of reproductive age have recurrent emotional and physical symptoms in association with the menstrual cycle, particularly during the late luteal (premenstrual) and menstruation phases. These symptoms may interfere with social and occupational functioning, as well as with sleep; women who have menstrual-related problems are between two and three times more likely than other women to report insomnia and excessive sleepiness during the day [1]. This article reviews studies that have investigated sleep in women who suffer from significant menstrual-related disturbances, particularly premenstrual syndrome (PMS) and physical pain that occurs in association with menstruation (primary dysmenorrhea). It also discusses specific sleep disorders that are related to the menstrual cycle: premenstrual insomnia and premenstrual hypersomnia.

An important issue when investigating conditions characterized by recurring bouts of symptoms is whether group differences in measured variables between patients and controls occur only in association with symptom occurrence or whether they also are present when the patients are asymptomatic. In the present context, the persistence of group differences across all phases of the menstrual cycle would argue for the existence of an underlying trait difference, perhaps associated with some subclinical symptom presentation, which manifests clinically when an additional stressor such as menstruation (or the hormonal changes associated with menstruation) is present. Group differences that occur only in conjunction with symptoms are more likely to reflect state-related phenomena. The determination of trait versus state differences may provide insight into the underlying mechanisms of

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the pathology and guide the nature and timing of appropriate treatment.

Premenstrual syndrome and premenstrual dysphoric disorder

Definitions and etiology

The definition of PMS varies in the literature [2] but generally is characterized by "emotional, behavioral, and physical symptoms that occur in the premenstrual phase of the menstrual cycle, with resolution after menses" [3]. PMS is classified in the International Classification of Diseases under "pain and other conditions associated with female genital organs and menstrual cycle" [4]. Many women of reproductive age experience some physical or emotional symptoms premenstrually, but approximately 22% of women have moderate to severe premenstrual symptoms that they perceive as distressing and that impact their work and/or social relationships [5]. Premenstrual dysphoric disorder (PMDD, previously known as "late luteal phase dysphoric disorder") is a severe form of PMS that occurs in 3% to 8% of women [6]. PMDD is classified as a "depressive disorder not otherwise specified" in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) [7]. A diagnosis of PMDD requires the occurrence of five specified symptoms, of which at least one must be a mood-related symptom, during the late luteal phase, for at least two consecutive cycles (Box 1) [7]. Diagnostic criteria for PMS are not so clearly defined; the difference between PMS and PMDD lies in the minimal number of symptoms required for diagnosis. Both severe PMS and PMDD are associated with significant functional impairment with an impact on quality of life [8].

Several instruments have been developed to assess PMS/PMDD. Ideally, assessment should be made prospectively using daily symptom reports to document accurately an increase in symptom expression and severity during the late luteal phase compared with the early/mid-follicular phase [8]. Confirmation of a PMDD diagnosis requires prospective documentation of symptoms over two menstrual cycles [7]. With prospective evaluation of symptoms, it also is possible to rule out pre-existing, underlying psychiatric disorders, which is of particular importance given the high comorbidity of PMDD and depressive disorders [9]. Women who participate in studies of PMS and PMDD therefore need to go through rigorous and lengthy screening procedures.

Although the cause of PMS and PMDD remains unknown, biologic, psychosocial, and biopsychosocial hypotheses have been proposed. There is

Box 1: Research criteria for premenstrual dysphoric disorder

- A. In most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):
 - (1) markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
 - (2) marked anxiety, tension, feelings of being "keyed up" or "on edge"
 - (3) marked affective lability (eg, feeling suddenly sad or tearful or increased sensitivity to rejection)
 - (4) persistent and marked anger or irritability or increased interpersonal conflicts
 - (5) decreased interest in usual activities (eg, work, school, friends, hobbies)
 - (6) subjective sense of difficulty in concentrating
 - (7) lethargy, easy fatigability, or marked lack of energy
 - (8) marked change in appetite, overeating, or specific food cravings
 - (9) hypersomnia or insomnia
 - (10) a subjective sense of being overwhelmed or out of control
 - (11) other physical symptoms, such as breast tenderness or swelling, headache, joint or muscle pain, a sensation of "bloating," weight gain
- B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others (eg, avoidance of social activities, decreased productivity and efficiency at work or school).
- C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as Major Depressive Disorder, Panic Disorder, Dysthymic Disorder, or a Personality Disorder (although it may be superimposed on any of these disorders)
- D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles. (The diagnosis may be made provisionally before this confirmation).

(From Diagnostic and statistical manual of mental disorders. 4th edition. Text revision. Washington, DC: American Psychiatric Association, 2000. p. 717-8; with permission.)

evidence suggesting that women who have PMS may be more sensitive to usual changes in gonadal hormones such as estrogen and progesterone [10]. Abnormalities in the serotonin neurotransmitter system [6,11] and in the GABAergic system [12–14] also have been linked with the development of premenstrual symptoms. Some theories related to the cause of premenstrual symptoms are multifaceted and include the relationship between biologic, social, and psychologic factors [15]. For example, it is suggested that some women have a predisposition to the development of premenstrual symptoms and syndromes [6] and that such biologic vulnerabilities interact with environmental factors and stresses that are present during the luteal phase [16], leading to the development of premenstrual symptoms [6].

Sleep disturbances

Among the most common symptoms reported by women who have PMS are problems with sleep [17]. Women who have PMS typically report sleep-related disturbances, such as insomnia and disturbing dreams or nightmares, during the premenstrual phase [18]. Further, sleep disturbance (hypersomnia or insomnia) is listed as one of the defining criteria for a diagnosis of PMDD in the DSM-IV (Box 1).

Mauri and colleagues [19] conducted the first detailed study of sleep disturbances in women who have PMS. Assessment of sleep quality and premenstrual symptoms was based on retrospective self-reports from 14 patients attending a PMS clinic, which were compared with controls. Women from the PMS clinic group reported having more unpleasant dreams, tossing and turning, frequent awakenings, and needing a long time to fall back asleep after an awakening during the night when they were experiencing premenstrual symptoms in the late luteal phase. A subsequent small, prospective laboratory study ($n = 9$) indicated that PMS clinic patients seemed to have more awakenings, body movements, and morning tiredness in the luteal and menstruation phases, but details of the study were not provided [18]. Parry and colleagues [20], however, found no differences between the late luteal phase and the follicular phase in sleep time or time spent awake, as recorded in daily sleep logs, in a group of 23 patients who met criteria for a diagnosis of PMDD. Patients reported less sleep than controls, however, in both the asymptomatic follicular and symptomatic luteal phases of the menstrual cycle. A recent study in a small group of nine women who had severe PMS or PMDD based on prospective ratings also found no menstrual-phase difference in self-reported total sleep time [21]. The women, however, rated their sleep

quality, measured on a 100-mm visual analogue scale, as significantly poorer during the late luteal phase (56 ± 15 mm) than during the asymptomatic follicular phase (73 ± 12 mm) [21]. Women who had more severe depression ratings were more likely to rate their sleep quality as poorer (Fig. 1). Other studies have found that even women who do not have significant premenstrual symptoms may rate their sleep quality as poorer in the late luteal phase than in the follicular phase [22,23]; however the degree of change seems to be less than that of women who have severe PMS [21].

Taken together, findings suggest that women who have severe PMS or PMDD perceive their sleep to be more disturbed in association with other premenstrual symptoms, although not necessarily in association with increased perceived time spent awake during the night and not necessarily limited to the time when they are experiencing PMS symptoms. It should be emphasized, however, that only 55 women with PMS have been studied in terms of their subjective experience of sleep, and that variable disease definitions and methodologies were used.

Studies using objective polysomnographic (PSG) recordings have shown little evidence of nocturnal sleep disturbance that is specific to premenstrual symptom expression in the late luteal phase compared with other phases of the menstrual cycle [18,21,24–28]. Sleep efficiency (percentage of sleep time relative to time in bed) and wakefulness after sleep onset are similar in women who have PMS or PMDD and women who have minimal symptoms in the late luteal phase [21,24–28]. Although differences in sleep architecture between the late luteal phase and the follicular phase have been found,

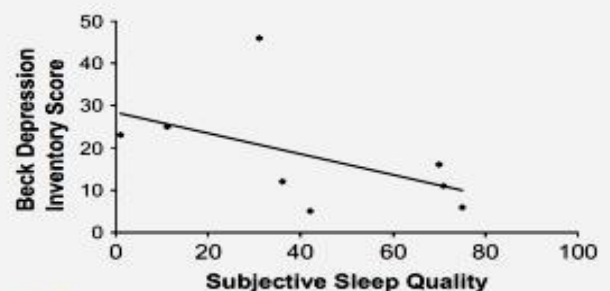


Fig. 1. Scatterplot and regression line of scores on the Beck Depression Inventory versus subjective sleep quality ratings (rated on a visual analogue scale; higher numbers denote better sleep quality) in eight women who had severe PMS during the late luteal phase of the menstrual cycle ($r^2 = 0.5$; $P = .05$). (From Baker FC, Kahan TL, Trinder J, et al. Sleep quality and the sleep electroencephalogram in women with severe premenstrual syndrome. *Sleep* 2007;30(10):1283–91.)

these differences are evident in groups of women who suffer from PMS as well as in those who do not (control groups) [21,25–28] and therefore cannot be attributed solely to PMS.

Some differences in nocturnal sleep architecture have been noted between women who have severe PMS or PMDD and women who have minimal symptoms. These differences, however, occur during both the follicular and luteal phases and are not consistent across studies. Lee [26] studied sleep, based on PSG recordings, in 13 women, 7 of whom met study criteria for PMS. Women were defined as being symptomatic for PMS if they showed at least a 30% increase in scores on the Profile of Mood States or in their 7-day average score on the Woods Women's Health Diary during the luteal phase compared with the follicular phase. Women who had PMS had significantly less slow-wave sleep than women did not have PMS in both the follicular and luteal phases of the menstrual cycle. The symptomatic group also had approximately 7% to 10% more stage 2 sleep than controls, which was statistically significant in the follicular phase [26]. Parry [27] found that eight patients who had severe PMS (based on prospective ratings over 2 months) also had significantly more stage 2 sleep, associated with a significant decrease in REM sleep, than did controls. These effects were evident in the early and late follicular phase as well as in the early and late luteal phase. A subsequent study by the same authors, however, found no differences in sleep architecture between 14 women who had PMDD and 9 controls studied in the follicular and late luteal phases [28]. Both subject groups had quite low sleep efficiencies (~80%) during recordings, possibly because of experimental conditions, which may have masked any group differences. As part of this study, women underwent a night of partial (early and late) sleep deprivation during their late luteal phase only. During recovery from sleep deprivation, group differences emerged: women who had PMDD had better sleep quality with a shorter sleep-onset latency, less wakefulness after sleep onset, a higher sleep efficiency, and less stage 1 sleep than controls [28]. The authors suggest that sleep deprivation might help restore a healthier circadian regulation of sleep in women who have PMDD [28]. Finally, a recent study found that nine women who had severe PMS or PMDD, determined from prospective ratings, had a longer latency to REM sleep than 12 controls, regardless of menstrual-cycle phase [21].

These inconsistent findings between studies paint a confusing picture as to whether trait-like alterations in sleep architecture are a component of severe PMS and what their relevance might be. Again, it needs to be emphasized that only a small

number of patients have been studied in a handful of studies, and variable results may be attributable to differences in methodology, such as instruments used to diagnose PMS and PMDD, time of recordings during the luteal phase, variable (and generally small) sample sizes, and the reliance on Rechtschaffen and Kales [29] criteria for scoring sleep stages, which do not allow the quantification of changes in the microstructure of sleep. The different findings also may be a consequence of variations in the types of symptoms experienced by women who have PMS, with some women experiencing irritability and anxiety as core symptoms and others reporting depression as the core symptom [30].

One study that performed a more detailed analysis of sleep EEG microarchitecture (power spectral analysis and period amplitude analysis) in women who had severe PMS found no differences in the sleep EEG during the late luteal phase compared with the follicular phase that were specific to the PMS group [21]. Women who had PMS, however, showed some trait-like differences across the menstrual cycle with decreased incidence of delta waveforms, increased incidence and amplitude of theta waveforms, and a tendency for increased spectral power in the lower sigma frequency band in non-REM sleep compared with controls [21]. These findings suggest that there may be subtle trait-like differences in sleep architecture and sleep EEG activity in women who have severe PMS that persist in the absence of PMS symptoms. Because this study included only nine women who had severe PMS or PMDD, these findings need to be replicated and confirmed in a larger group.

In summary, women who have severe PMS are likely to report a subjective experience of poorer sleep quality in association with their other premenstrual symptoms. To date, however, studies have not found disturbances in sleep architecture based on PSG recordings or observations of sleep EEG that are specific to premenstrual symptom expression. Possibly, women who have PMS may be more sensitive to subtle changes in sleep architecture that occur in all women during the luteal phase and particularly during the late luteal phase (see [31] for review). For example, some studies have found an increase in intermittent wakefulness [27] or wake time [21], based on PSG recordings during the late luteal phase, in both women who have significant premenstrual symptoms and those who have minimal symptoms. This increase in sleep fragmentation may affect subjective ratings of sleep quality, particularly in women who have severe PMS. Alternatively, the decline in reported sleep quality in women who have PMS may be a consequence of a negative reporting bias in association with premenstrual symptoms [21]. A similar

tendency for negative evaluations of sleep quality has been reported for depressed patients [32] and patients who have irritable bowel syndrome [33].

Age may be a factor that influences the extent of sleep disturbance in association with premenstrual symptoms: preliminary findings indicate that women who have PMS aged 40 years and older report more frequent waking at night as well as more early waking than younger women [34]. Possible differences in sleep structure between women who have severe PMS and women who have minimal symptoms in both the follicular and luteal phases of the menstrual cycle need to be investigated further to determine whether they are linked with specific premenstrual symptoms, such as depressed mood.

Daytime sleepiness and alertness

If sleep disturbance plays a role in the development or exacerbation of PMS symptoms, there should be some measurable impact on daytime sleepiness. As with sleep itself, sleepiness can be assessed both in terms of its subjective experience or more objectively in terms of the propensity to fall asleep (usually measured in minutes) if given the opportunity to do so.

Women who have PMS commonly report sleepiness, fatigue, and an inability to concentrate during the premenstrual phase [18]. Few studies have investigated these symptoms in any detail. Manber and Bootzin [23] analyzed sleep and daytime diaries of 32 women between the ages of 27 and 51 years. At bedtime, the women rated various mood-related variables from which a premenstrual severity index was calculated; three women met criteria for severe PMS. Women also rated their sleepiness levels at bedtime. Sleepiness varied significantly with menstrual phase, being higher in the luteal phase, and the change from the follicular to luteal phase

correlated significantly with the premenstrual index. The authors suggest that women who have more severe symptoms of PMS may need more sleep during the late luteal phase [23]. This interesting possibility has not been tested with laboratory-based studies, because sleep-wake schedules typically are constrained in the laboratory.

Although the complete methodology of the study is not provided, Mauri [18] found that a group of nine PMS clinic patients had greater levels of daytime sleepiness, based on scores on the Stanford Sleepiness Scale [35] in the luteal and menstruation phases of the menstrual cycle. A recent study also used the Stanford Sleepiness Scale in addition to a Subjective Alertness Scale to investigate daytime sleepiness and alertness in women who had significant premenstrual symptoms [25]. Women who had significant symptoms were sleepier and less alert in the late luteal phase than in the follicular phase, whereas no menstrual-phase change in sleepiness was found in a group of women who had minimal symptoms (Fig. 2). In addition, women who had more severe symptoms were significantly sleepier and less alert than women who had minimal symptoms during the late luteal phase but not during the follicular phase of the cycle. Preliminary results from another study showed that women with PMDD had slower reaction times, along with a tendency to feel sleepier, than controls in their late luteal phase [36]. One study has used a nap protocol to investigate daytime sleep characteristics of women in the late luteal phase. Lamarche [25] found no significant differences in sleep architecture during a short mid-afternoon nap between young adult women who had severe and minimal premenstrual symptoms, although two women who had severe symptoms entered REM sleep,

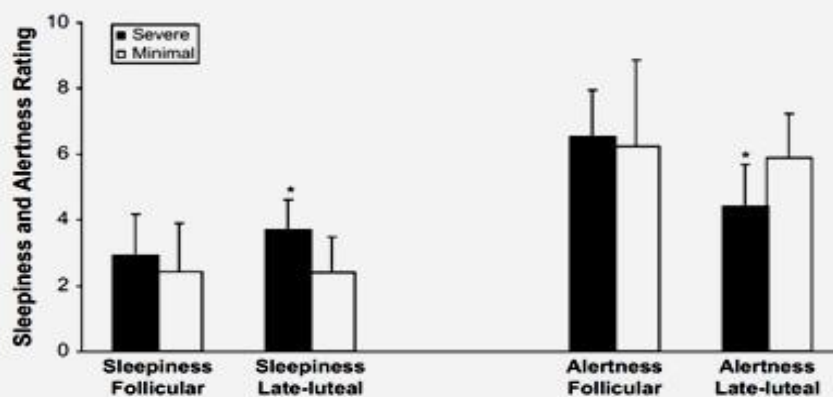


Fig. 2. Levels of sleepiness (rated on the Stanford Sleepiness Scale; higher numbers denote increased sleepiness) and alertness (rated on a Subjective Alertness Scale; lower numbers denote decreased alertness) for 10 women who had severe and 9 women who had minimal premenstrual symptoms during the follicular and late luteal phases of the menstrual cycle. Women who had severe premenstrual symptoms were significantly sleepier and less alert than women who had minimal

symptoms in the late luteal phase. *, $P < .05$. (From Lamarche L, Driver HS, Wiebe S, et al. Nocturnal sleep, daytime sleepiness, and napping among women with significant emotional/behavioral premenstrual symptoms. *J Sleep Res* 2007;16(3):262–8.)

whereas none of the women who had minimal symptoms did so. Of note, there were no group differences in sleep-onset latency: the group that had severe premenstrual symptoms fell asleep in 6 minutes, on average, and the group that had minimal symptoms fell asleep in 7 minutes, on average. The short sleep-onset latency found for both groups of women suggests that there was a high sleep need during the late luteal phase regardless of symptom severity, possibly indicating chronic sleep restriction, as may be expected in this age group (mean age 26.7 years) [37].

Although the number of studies is limited, findings indicate that sleepiness is a recognizable component of severe PMS. Because studies show that objective sleep disturbances are minimal in women who have PMS during their late luteal phase, it remains to be determined what factors contribute to the increase in daytime sleepiness.

Circadian rhythm disturbances

Although studies have not been conducted under constant routine conditions, evidence suggests that women who have PMDD may have abnormal regulation of their circadian rhythms. High mean nocturnal temperatures have been reported in women who have severe PMS or PMDD compared with asymptomatic controls, regardless of menstrual-cycle phase [38]. In a larger study, no significant differences were found in temperature amplitude, minimum temperature, or timing of the temperature minimum, although women with PMDD tended to have higher mean nocturnal temperatures than controls [39]. During partial sleep deprivation in the late luteal phase, group differences emerged. Women with PMDD had higher temperature maxima and mesors (rhythm-adjusted mean) than women who had minimal symptoms [39]. Also, women with PMDD had a delayed temperature acrophase (time at which the peak of the rhythm occurs), whereas controls had an advanced acrophase during early sleep deprivation (sleep from 03:00 to 07:00) compared with a baseline recording in the late luteal phase [39]. These timing disturbances in women with PMDD may reflect underlying disturbances in the circadian pacemaker that regulates the temperature rhythm [39].

Disturbances in melatonin rhythms and in the timing of the rhythms of cortisol and thyroid-stimulating hormone also have been reported in women with PMDD [40–43]. Parry and colleagues [40] found that women with PMDD had a phase-delayed melatonin onset in the luteal phase compared with the follicular phase, an effect not found in controls. Also, area under the curve, amplitude, and mean level of melatonin were decreased during the luteal phase compared with the follicular phase

in women with PMDD and compared with controls [40]. A study by Shinohara and colleagues [44] examined the timing of sleep onset during the luteal and follicular phases of the menstrual cycle in one participant who had PMS. Results showed that sleep onset was advanced after menstruation had begun but then was progressively delayed shortly after ovulation until the next menstruation. The follicular phase therefore was characterized by a phase advance, whereas the luteal phase was characterized by a phase delay.

Given these possible disturbances in circadian rhythmicity in women with PMDD, investigators have explored the possibility of treating PMDD by manipulating the timing of sleep with sleep-deprivation protocols (as described later) or with light therapy. Appropriately timed light therapy has shown some promise as a treatment strategy for PMDD, possibly by altering nocturnal melatonin secretion [45,46]. Bright light therapy significantly reduced depression, irritability, and physical premenstrual symptoms compared with a placebo condition, and these improvements were maintained at 12 months [47]. Similarly, Lam and colleagues [48] found that 30 minutes of light therapy in the evening for 2 weeks during the luteal phase resulted in a significant improvement in premenstrual symptoms in women who had PMS compared with baseline levels. These initial findings are promising; however, a meta-analysis of clinical trials of bright light therapy concluded that larger trials are needed to define the role bright light therapy might have in the treatment of PMDD [49].

Sleep deprivation studies

Sleep deprivation has been shown to be effective in reducing depressive symptoms in patients who have major depressive disorder [50]. Given the similarities between PMDD and other mood disorders, such as depression [51], it is of interest to investigate whether sleep deprivation has a similar efficacy in this population. Parry and colleagues have conducted studies to determine the effects of various sleep-deprivation protocols on mood variables in women who have severe PMS or PMDD [20,52]. Parry and Wehr [52] examined the effects of total sleep deprivation (40 hours) during the late luteal phase on the symptoms of women who had premenstrual depression. Eight of 10 women experienced an improvement in premenstrual mood, based on Hamilton ratings, with total sleep deprivation, and the improvement was maintained after a recovery night's sleep. Two consecutive nights of late-night sleep deprivation (sleeping from 20:00 to 02:00) were found to be more effective than early sleep deprivation (sleeping from 02:00 to 08:00) and were as effective as total sleep deprivation [52].

In a subsequent larger study of 22 women who had PMDD and 17 controls, no differences were found between the effectiveness of 1 night of early (sleep from 03:00 to -07:00) versus 1 night of late (sleep from 21:00 to 01:00) sleep deprivation [20]. Both types of partial sleep deprivation had similar positive effects on mood in 60% to 67% of patients, but these effects were significant only after recovery sleep [20]. Predictors of responsiveness to sleep deprivation were sadness and depression, duration and severity of symptoms, history of depression, and personal and family history of suicide. Of interest, changes in REM latency and REM density in the first REM sleep period from baseline to recovery nights were significantly correlated with improvement in mood in responders to sleep deprivation [28].

The effect of sleep deprivation on mood in women with PMDD differs from that found in patients with major depressive disorder, who have improved mood the day following total sleep deprivation but tend to relapse after recovery sleep [50]. The lack of relapse after recovery sleep in women with PMDD makes partial sleep deprivation a potential treatment option for PMDD [20]. Indeed, a follow-up study of seven patients who continued with the treatment of 1 night of partial sleep deprivation at home when they were symptomatic in their luteal phase showed that the deprivation protocol continued to be effective in improving mood in these women [20]. Although these studies show promise, several unanswered questions need to be addressed before sleep deprivation can be considered as a potential treatment strategy for PMDD. For example, it still remains to be determined whether the positive response to sleep deprivation is more than just a placebo effect; if there is a critical window when the sleep-deprivation protocol should be applied to be effective; and if the positive effects of a single night of sleep deprivation can be maintained throughout the late-luteal phase.

In summary, there is evidence that disturbances in sleep and circadian regulation are components of severe PMS and PMDD and that correcting these disturbances with bright light therapy or sleep deprivation may have positive effects on mood. Many findings are preliminary, and there is a need for further study. Future studies need to be more consistent in their assessment measures as well as in their inclusion/exclusion criteria for study participants.

Primary dysmenorrhea

Definition and etiology

Dysmenorrhea, defined as painful menstrual cramps of uterine origin, is the most common gynecologic condition among women of reproductive

age [53] and is very severe in approximately 10% to 25% of women [54,55]. Despite its common occurrence, it is underdiagnosed and undertreated. Based on pathophysiology, dysmenorrhea can be classified as either primary or secondary [56]. Primary dysmenorrhea is defined as painful, spasmodic cramping in the lower abdomen, just before and/or during menstruation, in the absence of any discernable macroscopic pelvic pathology [54]. The onset of primary dysmenorrhea usually occurs in adolescence, at or shortly after (6–24 months) menarche [55]. Primary dysmenorrheic pain is most severe during the first or second day of menstruation and typically lasts for 8 to 72 hours [57]. The pain may radiate to the back and thighs and is frequently accompanied by systemic symptoms including nausea, vomiting, diarrhea, fatigue, and insomnia [55,58]. Secondary dysmenorrheic pain, in contrast, may originate from a number of identifiable pathologic conditions including endometriosis, adenomyosis, fibroids (myomas), and pelvic inflammatory disease.

The etiology of primary dysmenorrhea is not entirely understood, but prostaglandins have been implicated as the primary mediators of the pain [54]. Prostaglandins are thought to produce the ischemic pain experienced by women who have dysmenorrhea by causing contraction of the uterine muscle or constriction of uterine blood vessels; both of which ultimately reduce the blood supply to the uterus. Alternatively, prostaglandins may reduce the nerve ending's threshold for pain perception [55,53]. Given the prostaglandin-based origin of primary dysmenorrhea, the most common pharmacologic treatment for dysmenorrhea is nonsteroidal anti-inflammatory drugs (NSAIDs) [59].

Primary dysmenorrhea has characteristics of both chronic and acute pain syndromes: the pain recurs monthly, and, although the pain is severe, it is of short duration with a predictable onset and offset. The painful menstrual cramps experienced by these women every month significantly impact productivity and quality of life [60].

Sleep disturbances

Based on survey data, menstrual cramps are a major disruptor to sleep in women of reproductive age [61]. As far as the authors are aware, only one published study has systematically investigated the impact of dysmenorrheic pain on sleep [62]. The study included 10 women who had primary dysmenorrhea and 8 women who did not have dysmenorrhea (controls) who were studied in the sleep laboratory on the first night of menstruation as well as during the mid-follicular and mid-luteal phases of the menstrual cycle. Although not prospectively documented, none of the women reported significant

symptoms of PMS. The women who had primary dysmenorrhea rated their menstrual pain as severe in the evening before going to bed on the first day of menstruation. As shown in Fig. 3, in association with their pain, the dysmenorrheic women (48 ± 24 mm) rated their sleep quality as significantly worse than controls (65 ± 21 mm) during menstruation and compared with their own pain-free follicular and luteal phases [62]. PSG recordings also indicated significant sleep disturbance in the women who had dysmenorrhea. They had a lower sleep efficiency, increased combined time spent awake, moving, and in stage 1 light sleep, and less REM sleep compared with pain-free phases of the menstrual cycle and compared with women who did not suffer from menstrual pain [62]. Four of the women who had dysmenorrhea required pain-relieving medication (mefenamic acid) before their overnight recordings; these women may have experienced even greater sleep disruption in the absence of medication.

Given that NSAIDs are an effective treatment for dysmenorrhea [56], it is likely that treatment of nocturnal pain with NSAIDs would alleviate painful cramps and consequently improve sleep quality in women who have dysmenorrhea. Indeed, Iacovides and colleagues have preliminary evidence that women who have primary dysmenorrhea have a better sleep efficiency and subjective sleep quality when their pain is treated with a NSAID compared with placebo (Stella Iacovides, BSc (Hons), Johannesburg, South Africa, unpublished findings, June 2007).

There is some evidence that women who have dysmenorrhea may have altered sleep architecture even before the onset of pain. Dysmenorrheic women were found to have significantly less REM sleep (in association with higher nocturnal rectal temperatures) compared with controls, during the follicular, luteal, and menstruation phases of the menstrual cycle [62]. A subsequent study that investigated sleep and body temperatures in the follicular and luteal phases of the menstrual cycle in women who had dysmenorrhea and controls (eight women in each group) did not support this finding; there were no differences in the 24-hour temperature rhythms or in REM sleep between women who had dysmenorrhea and controls [63]. Sample sizes were small in both these studies, and it remains to be confirmed whether there are any significant differences in sleep and body temperature in women who have primary dysmenorrhea outside of the painful menstruation phase.

Menstrual-associated sleep disorder

Two sleep disorders that are temporally related to menstruation, premenstrual insomnia and

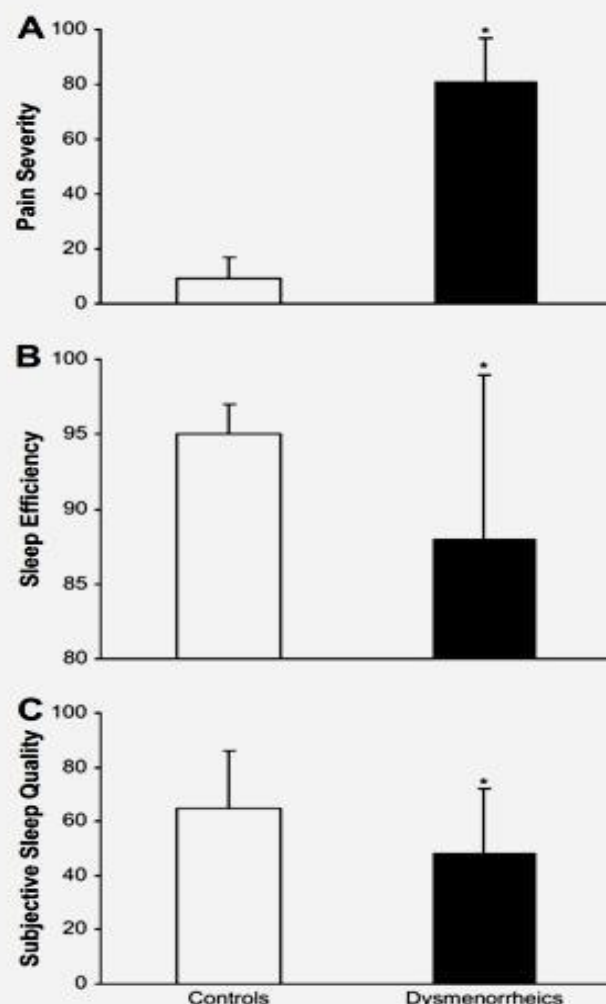


Fig. 3. (A) Pain severity (rated on a visual analogue scale; higher numbers denote greater pain), (B) PSG-defined sleep efficiency, and (C) subjective sleep quality (rated on a visual analogue scale; higher numbers denote better sleep quality) in 10 women who had primary dysmenorrhea and in 8 women who had minimal symptoms on the first night of menstruation. *, $P < .05$. (Data from Baker FC, Driver HS, Rogers GG, et al. High nocturnal body temperatures and disturbed sleep in women with primary dysmenorrhea. *Am J Physiol* 1999;277(6 Pt 1):E1013–21.)

premenstrual hypersomnia, have been proposed in the International Classification of Sleep Disorders [64]. Both of these disorders are rare and have been characterized based on case studies. Importantly, a diagnosis of menstrual-associated sleep disorder is given only if the patient does not meet the criteria for a diagnosis of PMDD.

Premenstrual insomnia is characterized by difficulty in falling asleep or remaining asleep in

temporal association with the menstrual cycle. This form of insomnia occurs in the week before the onset of menses and must be present for at least three consecutive months for a diagnosis to be given. The cause of premenstrual insomnia is unknown, but there is some evidence from a case study suggesting that desynchronization of temperature and sleep-wake rhythms in the luteal phase could be a contributing factor [65].

Premenstrual hypersomnia is characterized by sleepiness occurring in the week before the onset of menses. The patient has no complaints of persistent, excessive sleepiness at other times in the menstrual cycle [64]. Some case studies of women who have premenstrual hypersomnia have been published [66–68]. Polygraphic recordings in one patient (13 years old) indicated a 44% increase in total sleep time in a 24-hour period, with a decrease in the percentage of slow-wave sleep and increases in stage 1 and stage 2 sleep but no change in the organization of night-time sleep stages when the patient was symptomatic compared with asymptomatic intervals [67]. Patients who have premenstrual hypersomnia have been treated successfully with estrogen [67] or oral contraceptives [68].

Summary

Menstrual cycle-related pathology has a high prevalence and at least putative links to sleep disturbance and/or daytime sleepiness. Nonetheless, the relationship between sleep and these disorders has been studied in only a very few patients and studies. This paucity is not unsurprising, because such studies have to overcome three major obstacles to research funding. First, although they are debilitating and even potentially personally devastating in terms of their impact on the sufferers, menstrual-related disorders are not life-threatening conditions; second, it often is difficult to convince funding agencies of the importance of sleep as a factor in problems that manifest as daytime symptoms; and third, these problems are “women’s issues.”

PMS/PMDD demonstrates a trait-like pattern of subtle alterations in sleep architecture and sleep EEG that persists across symptomatic and asymptomatic phases of the menstrual cycle. There is, however, a clear increase in daytime sleepiness in the symptomatic late luteal phase. This dissociation of objective sleep quality from sleepiness is a salutary indicator to sleep researchers that sleepiness is not necessarily linked to poor sleep quality, as it is traditionally measured in the laboratory. Given the preliminary evidence presented in this article that PMS/PMDD may be associated with some form of circadian dysregulation, the sleepiness may be a function of desynchronization of

circadian rhythms. Put in terms of Borbely’s two-process model of sleep regulation [69], PMS/PMDD could be conceived as being a “Process C” problem rather than a “Process S” problem. This view is supported by the evidence of partial sleep deprivation being a possible treatment of PMS/PMDD symptoms.

It should be self-evident from the material presented that more research is warranted, with continuous routine studies to unmask underlying circadian rhythms effectively and studies to identify subject characteristics that predict treatment efficacy of sleep deprivation as well as determination of the optimal sleep-deprivation protocol for women to use to obtain symptom relief.

It is important to consider the presence of menstrual-associated disorders when evaluating women who have sleep complaints to determine whether there is an association between their sleep disturbance and the menstrual cycle. It also is important for future research studies to assess sleep-related interventions as preventative measures for PMS symptoms and sleep disruptions and to determine that analgesic treatment regimens for menstrual pain do not negatively impact sleep quality.

It is rare to find such a mismatch between the small number of studies investigating a problem and the high prevalence of that problem in society. In this case, the overused and sometimes trite conclusion that “clearly more work needs to be done” is not only warranted but self-evident.

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