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PELVIC PAIN DUE TO ENDOMETRIOSIS AND DYSMENORRHEA

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Pelvic pain due to endometriosis and dysmenorrhea

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Lisa Söderman

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ABSTRACT

Background

Approximately 70% of women in reproductive age suffer from dysmenorrhea around the world but no prevalence study has been made in Sweden for 35 years. Dysmenorrhea, painful menstruation, can be a sign of endometriosis which for many is a disabling disease due to pelvic pain but also symptoms from the gastrointestinal tract, the bladder, fatigue and infertility. Treatment options for this chronic inflammatory disease as well as for dysmenorrhea are pain killers and hormonal therapy to suppress the menstrual cycle, and for endometriosis sometimes surgery. But these treatment options are not suited for everybody and are often associated with adverse effects. Preclinical trials have shown that melatonin has analgesic and anti-oxidative properties. Melatonin has shown to reduce the size of endometriotic implants in rodents. A clinical trial has showed melatonin to reduce endometriosis-associated pain more effectively than placebo.

Aim

To investigate the prevalence of dysmenorrhea and its impact on the life of young women in Stockholm.

To investigate the analgesic effect of melatonin on severe dysmenorrhea and endometriosis-associated pain respectively, compared to placebo. A significant clinical effect was set to a reduction of 1.3 units on the numeric rating scale.

Materials, methods and results

Three studies were conducted during 2017-2021. Study I is a cross-sectional study. A questionnaire was sent out to all women born in the year 2000 and residing in Stockholm (n= 3998). With a response rate of 45%, the prevalence of dysmenorrhea was 89% (1580 of 1785, 95% CI 87-90), out of which 36% (574 of 1580, 95% CI 34-39) reported severe dysmenorrhea. High rates of fatigue (83%) and headache (82%) were observed, 14% reported monthly absenteeism and the tendency to seek medical care was low as only 7% had seen a doctor.

Studies II and III are placebo-controlled, randomized trials with 40 women in each trial, 20 were allocated to placebo and 20 to melatonin. In Study II women with severe dysmenorrhea received 10 mg melatonin or placebo at bedtime for the week of menstruation during two menstrual cycles. No superior analgesic effect was seen with melatonin compared with placebo.

In study III women with endometriosis-associated pain received 20 mg melatonin or placebo at bedtime for two consecutive menstrual cycles or months. No superior analgesic effect was seen with melatonin compared with placebo.

Conclusions

The prevalence of dysmenorrhea in Stockholm is high with substantial implications on the daily lives of young women. The low tendency to seek medical care suggests a normalization.

Our chosen dose and regime could not show any analgesic effect superior to placebo, future studies are needed to investigate other doses and regimes that could be of use as adjuvant treatment of dysmenorrhea and endometriosis-associated pain.

LIST OF SCIENTIFIC PAPERS

I. **Prevalence and impact of dysmenorrhea among Swedish adolescents**

Söderman L, Edlund M, Marions L

Acta Obstet Gynecol Scand. 2019 Feb;98(2):215-221

II. **Adjuvant use of melatonin for pain management in dysmenorrhea - a randomized double-blinded, placebo-controlled trial**

Söderman L, Edlund M, Böttiger Y, Marions L

Eur J Clin Pharmacol. 2021 Oct 20 doi: 10.1007/s00228-021-03234-6. Online ahead of print.

III. **Adjuvant use of melatonin for pain management in endometriosis - a randomized double-blinded, placebo-controlled trial**

Söderman L, Böttiger Y, Edlund M, Järnbert-Pettersson H, Marions L

Submitted

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LIST OF ABBREVIATIONS

Cmax	Maximum concentration
CANTAB	Cambridge Neuropsychological Test Automated Battery
COC	Combined oral contraceptives
COX	Cyclooxygenase
CPP	Chronic pelvic pain
CYP1A2	Cytochrome P450 Family 1 Subfamily A Member 2
DAG	Direct acyclic graph
EAPP	Endometriosis-associated pain
EHP-30	Endometriosis Health Profile-30
GnRH	Gonadotropin-releasing hormone
ISI	Insomnia Severity Index
ITT	Intention to treat
LT	Leukotrienes
MT1/MT2	Melatonin receptor 1/ Melatonin receptor 2
NRS	Numeric rating scale
NSAID	Non-steroid anti-inflammatory drug
PBAC	Pictorial blood loss assessment chart
PCS	Pain Catastrophizing Scale
PG	Prostaglandins
PP	Per protocol
QoL	Quality of life
RCT	Randomized controlled trial
TENS	Transcutaneous electric nerve stimulation
VAS	Visual analogue scale

1 INTRODUCTION

The definition of a public health concern is that it affects at least 1 % of the population [1]. Dysmenorrhea is a far more common disorder affecting and disabling many women. A recent meta-analysis found that 71% of young women, in studies from all over the world, suffer from dysmenorrhea and 20% had reported absenteeism from school due to dysmenorrhea [2] . The prevalence of dysmenorrhea in Sweden was last assessed 1982 in Gothenburg, when Andersch and Milsom showed a prevalence of dysmenorrhea of 72% in 19-year-old women, out of whom 15% reported severe dysmenorrhea [3].

Severe dysmenorrhea is associated with transformation to chronic pelvic pain [4] and can be a sign of endometriosis [5]. Endometriosis is a chronic inflammatory disease many times of a progressive character and is also associated with chronic pelvic pain. Two thirds of women with endometriosis experienced the first symptoms before the age of 20 [6] which highlights the importance of adequate treatment in girls and young women with dysmenorrhea. The treatment of dysmenorrhea and endometriosis is not only for reducing suffering but may also quell progression to chronic pelvic pain.

The available treatments are non-curative aiming to relieve symptoms but they are associated with side effects and are not compatible with the wish to conceive. Both dysmenorrhea and endometriosis are associated with chronic pelvic pain [4,7] and a lower quality of life [8,9].

Features of endometriosis are excessive estrogen stimulation, immune dysfunction, and angiogenesis. Pre-clinical studies show that melatonin can target those exact features and that there are melatonin receptors in the endometriotic cell. Anxiolysis and analgesia are other properties of melatonin which are desirable for treating dysmenorrhea with or without endometriosis.

The aim of this thesis is to provide an up-to-date assessment of the prevalence of dysmenorrhea and its impact on young women in Stockholm and to investigate the analgesic properties of melatonin on dysmenorrhea and on endometriosis-associated pain (EAPP).

2 BACKGROUND

2.1 DYSMENORRHEA

2.1.1 Prevalence and clinical presentation

Dysmenorrhea is the most common gynecological disorder amongst women of reproductive age, with a prevalence ranging between 45 and 95 % [10-12]. The great variance in prevalence between observational studies could be explained by biological differences, cultural taboo, cultural somatization or normalization and different perception of what classifies as dysmenorrhea and what is normal and not worth reporting. A meta-analysis from 2019 including 38 studies from different countries showed a prevalence of 71 % [2]. The studies have used different questionnaires but have all used numeric rating scale (NRS) or visual analogue scale (VAS). A standardized validated questionnaire for dysmenorrhea is lacking. Primary dysmenorrhea, painful menstruation without pelvic abnormalities, may be associated with vomiting, diarrhea, back pain, headache, dizziness, fatigue, sleeplessness, [13] and disturbed sleep [14]. The pain is typically lasts 8-72 hours, being most severe during the first or second day of the menstrual cycle [11]. Secondary dysmenorrhea is dependent on an underlying cause such as endometriosis, adenomyosis, myomas or pelvic inflammatory disease.

Risk factors for dysmenorrhea, both primary and secondary, include early age at menarche [15], long and heavy menstrual flow, high body mass index, family history of dysmenorrhea [16]. Symptoms of dysmenorrhea seem to decrease with age and parity. Pregnancies ending in spontaneous or induced abortion have shown no effect on the risk of dysmenorrhea [17,18]. Both Sundell and Knox found lower prevalence of dysmenorrhea in adults compared with adolescents in longitudinal studies [15,19].

Several studies suggest that dysmenorrhoic women have a hyper sensitization of pain fibers [20,21] and are more sensitive to noxious stimuli, even in pain free periods of time [21]. There are specific hypertrophic structural changes in the gray matter of the brain in women with dysmenorrhea, which could partially explain the hyperalgesia, whether those changes are cause or consequence is not known [22]. A meta-analysis shows that dysmenorrhea is positively correlated with chronic pelvic pain (CPP) and chronic non-pelvic pain e.g. headaches and fibromyalgia [4] (Fig. 1).

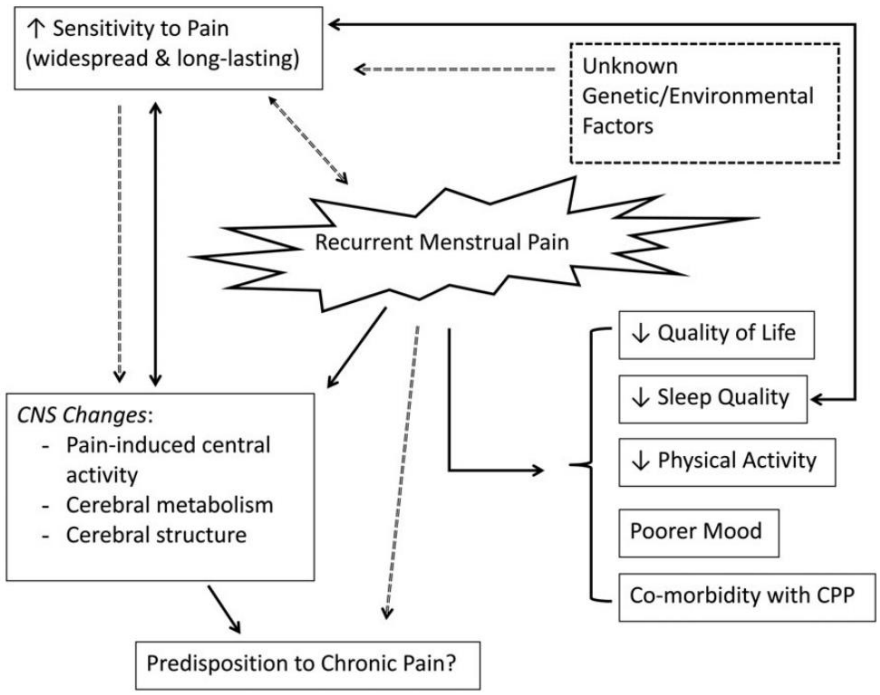

Figure 1. From Iacovides et al [16] illustrating the proposed (dotted lines) and known (solid lines) effects of recurrent dysmenorrhea.

Although there are differences in definition, between 10 and 33% of young women suffer from dysmenorrhea categorized as severe [3,23,24]. Quality of Life (QoL) has shown to be lower in women with dysmenorrhea compared to controls [8], with a correlation to the severity of dysmenorrhea [25].

Absenteeism has also shown a correlation with the severity of dysmenorrhea [23,24,26,27]. A meta-analysis with studies from several different countries states that 20 % of women were absent to some extent from school or university due to dysmenorrhea and that absenteeism was more common in low-income countries [2]. In some countries poor menstrual health or taboos will prevent girls from going to school during menstruation [28], rendering dysmenorrhea being one of many reasons for menstrual-related absenteeism.

In the US dysmenorrhea is the leading cause of short-term school absenteeism [29]. Few studies distinguish the level of recurrence of absenteeism, monthly absenteeism is reported by 12% of the participants in an Italian study [30] and by 1% in a Finnish study [23]. Previous studies have shown dysmenorrhea to have negative effects on academic and social performances [12,27].

Several studies have shown sub-therapeutic use of analgesics for these recurring pains amongst adolescents [31-33]. It is also known that there is a low tendency to seek medical advice for this condition [24], maybe due to the perception of dysmenorrhea being a normal condition rather than a disorder.

Dysmenorrhea is common, often severe, resulting in absenteeism from school and work but is yet undertreated and normalized (since it does not seem to be a condition worthy of a doctor's visit). There is no prediction model to identify which ones of the young women with dysmenorrhea that will develop chronic pain or have an early stage of endometriosis.

2.1.2 Pathogenesis

In a normal ovulatory menstrual cycle fatty acids, particularly arachidonic acids, are released after the withdrawal of progesterone prior to menstruation. This initiates a cascade of leukotrienes (LT) and prostaglandins (PG) released from the uterus which causes an inflammatory response, cramps and systemic symptoms [13]. In particular the PG F2α, cyclooxygenase (COX) metabolite of arachidonic acid causes potent vasoconstriction and myometrial contractions, leading to hypercontractility of the uterus, ischemia and pain [34] (Fig. 2). The severity of symptoms is directly proportional to the amount of PG released into the systemic circulation during sloughing of the endometrial lining [34,35].

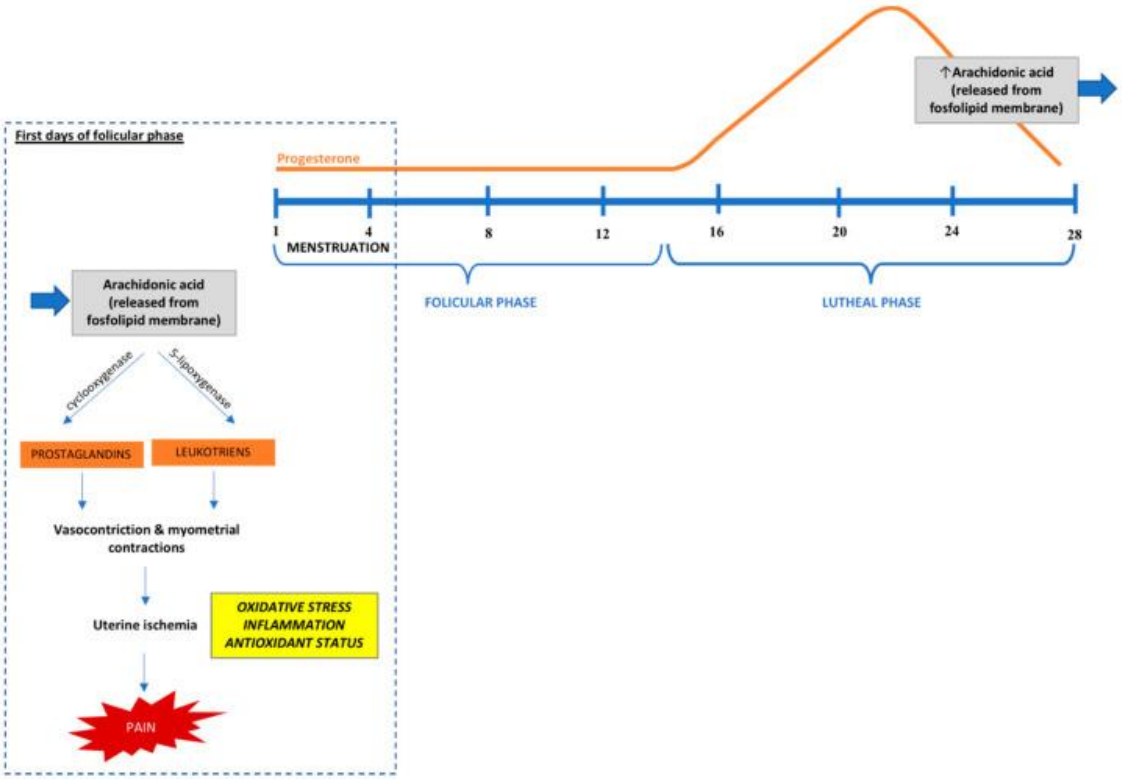

Figure 2 from Szmidt et al [36] illustrating the potential mechanism of inflammation in dysmenorrhea. During the first half of secretory (luteal) phase in the menstrual cycle, the level of progesterone increases, which has anti-inflammatory and regulating effects (prostaglandins and leukocytes synthesis) on the endometrial tissue. In the second half of the luteal phase, the progesterone level begins to fall, which causes the secretion of arachidonic acid and its metabolites, such as prostaglandins and leukotrienes.

However, there are women with dysmenorrhea showing non-elevated levels of PGF2α [37], suggesting the etiology is not being completely understood but leukotrienes and or platelet

activating factor may be involved [38]. A systematic review of six case-control studies indicated that the levels of oxidative stress markers were significantly higher in women with primary dysmenorrhea compared to controls. However, oxidative stress may also be modulated by lifestyle and environmental factors, such as diet, physical activity, alcohol consumption, smoking cigarettes, medical drug abuse, sleep deprivation, stress, or environmental pollution [36].

Four abnormalities regarding uterine contraction have been reported in women with primary dysmenorrhea [34]:

- elevated basal tone
- elevated active pressures
- higher frequency of contraction
- incoordinate uterine contractions during menstruation

Doppler studies show that higher pressure in the uterus affects the blood flow and causes painful myometrial ischemia. In asymptomatic women the contractions do not affect the blood flow [39].

2.2 ENDOMETRIOSIS

2.2.1 Prevalence and diagnosis

Severe dysmenorrhea can be a sign of endometriosis [5,40] which is a chronic, estrogen dependent, progressive disease due to ectopic location of endometrium, causing cyclic and acyclic pelvic pain as well as symptoms from the intestinal and urinary tract and infertility [7]. Prevalence is hard to evaluate due to the use of different diagnostic criteria, e.g. with or without histopathological examination. One review has suggested a prevalence between 6 and 11 % in the general female population [41], higher amongst those with CPP [42] or infertility [43]. A meta-analysis showed a prevalence of 62% upon laparoscopy in young women with CPP or dysmenorrhea [44]. However, prevalence of endometriosis in asymptomatic women of reproductive age has been shown to be 10-20% [45,46] diagnosed during laparoscopic sterilization and the possibility that some endometriotic lesions may represent a variant of normal has been suggested [47].

Endometriosis can be divided into four categories: superficial peritoneal endometriosis, deeply infiltrating endometriosis, endometriomas (ovarian cysts) and extra-genital endometriosis, according to rASRM (revised American Society for Reproductive Medicine) [48] and ENZIAN [49] which are two different staging systems. There are, however, 22 different classification and staging systems for describing endometriosis. A harmonization of the

classifications is ongoing but there is not yet a consensus [50]. Historically, laparoscopy with histopathology has been the gold standard for diagnosis, but now there is a tendency to try and diagnose endometriosis in a conservative manner through interviews, examination and imaging [51], unfortunately there is no consensus yet and no bio-markers available for diagnosis.

Recurring, chronic peripheral nerve activation can lead to central sensitization which can become autonomous and generate pain without peripheral noxious stimulus [52] which is why treatment should be initiated immediately without waiting for surgery or additional imaging.

Chronic pelvic pain is by definition perceived in the pelvic region and lasting for at least 6 months. "It is often associated with negative cognitive, behavioral, sexual and emotional consequences as well as with symptoms suggesting of lower urinary tract, sexual, bowel, pelvic floor or gynecological dysfunction", according to International association for the study of pain [53], which includes most cases of severe dysmenorrhea and endometriosis-associated pain. The prevalence of CPP among women of reproductive age in the UK is estimated to be 20 - 24% [54,55]. But all CPP is not endometriosis, a review found that only 28% of women with CPP had endometriosis [42]. Other causes are irritable bowel syndrome, bladder pain syndrome or interstitial cystitis and myalgias. Multiple pelvic pain syndromes often co-exists in the same patient [56]. The uterus, bowel and bladder share neural pathways with each other but also with skin, muscle, fascia and bones in the pelvis, this interconnection can explain the cross-sensitization between organs [57-59]. The location and extent of lesions seen during laparoscopy do not relate to location or intensity of pain experienced [60].

Approximately 50 % of those suffering from chronic pain have a co-morbid depression and/or anxiety disorder [61]. It has been shown that painful endometriosis is associated with negative effects on QoL and mental health compared to endometriosis without pain [9,62,63]. Women suffering from EAPP have reported implications on daily function, social interactions, sexuality, and psychological wellbeing [64]. The mean yearly cost for healthcare and managing endometriosis, including loss of productivity, was EUR 8 768/woman in Sweden in 2010 [65].

Higher risk for endometriosis has been reported for early age at menarche, short menstrual cycle length and heavy menstrual bleeding. Inverse association has been seen with greater parity [66].

The high prevalence of CPP not related to endometriosis and the high prevalence of asymptomatic endometriosis as well as the possibility of falsely negative findings in laparoscopy complicate diagnostics of endometriosis.

2.2.2 Pathogenesis

The patho-etiology of endometriosis is not fully known. The most common theory is retrograde menstruation and altered cellular immunity [67] [68]. But this does not explain the finding of premenarchal endometrial lesions in girls [69,70] or extra-pelvic lesions.
Other theories are:

- coelomic metaplasia where normal peritoneal tissue transforms into ectopic endometrial tissue [71]
- differentiation of stem/progenitor cells from bone marrow into endometriotic tissue [72]
- benign metastasis through lymphatic and/or hematogenous dissemination of endometrial cells [73,74]

It is unclear how and if the immune system is involved in initiation of endometriosis. Retrograde menstruation occurs in most women, but in women with endometriosis the immune system seems inapt to take care of the refluxed endometrial debris consisting of macrophages, erythrocytes, and apoptotic endometrial tissue and endometriotic lesions are established [75] or there could be abnormalities in the endometrial debris predisposing implantation and disease [76]. Endometriotic lesions secrete inflammatory mediators, and cause angiogenesis and neurogenesis. This triggers a cascade of events leading to fibrosis. Inflammation, alterations in peripheral and central pain receptors, endocrine changes, and structural alterations in the periphery and in the central nervous system may all contribute to EAPP [52]. The endometriotic lesion itself produces estradiol and prostaglandin through a positive feedback loop. The estradiol promotes survival, proliferation and inflammation in the poorly differentiated endometrial stromal cells. The prostaglandins cause inflammation and EAPP [77].
Women with endometriosis have inflammation in the peritoneal fluid, measured by higher levels of growth factors, proinflammatory cytokines, chemokines and oxidative proteins [78] than in non-endometriotic women. This milieu lowers the threshold for (sensitizes) sensory nerve fibers to generate or modulate pain [52] and amplifies the local inflammatory response and generation of pain [79] in a vicious cycle. It is currently well established that inflammation and oxidative stress have an interdependent relationship [80] and can cause

tissue damage [81]. There is a positive correlation with the level of advanced oxygen protein products and the pelvic pain symptom scores [82].
A recent meta-analysis confirm association with ovarian [83], thyroid and breast cancer [84]. There seem to be an association with hypothyroidism, fibromyalgia [85] and other autoimmune diseases [86] and also with ischemic heart disease [87] and coronary artery disease [88].

2.3 TREATMENT

The goal of the treatment of dysmenorrhea is to alleviate, or even eliminate, painful episodes. Not only to relieve suffering during the menstruation but reduction of recurrent pain may also as serve as prophylaxis for transformation into chronic pain.
The initial treatment regime for dysmenorrhea, as well as for endometriosis, is non-steroid anti-inflammatory drugs (NSAID) and/or hormonal suppression [89,90]. A Cochrane review states that NSAIDs give a stronger pain relief than placebo and acetaminophens. No superior effect with COX2-inhibitors compared with NSAID was shown [91]. By inhibiting endometrial prostaglandin production NSAIDs can also reduce menstrual blood loss [92]. Opioids should be avoided due to the high risk of addiction [93]. The risk for chronic opioid use may be even higher in women with endometriosis partially explained by the high prevalence of other pain-related and psychiatric co-morbidities [94]. Transcutaneous electric nerve stimulation (TENS) has been shown to be equally effective as the NSAID Naproxen in reduction of (primary) dysmenorrhea [95].
Tocolytic drugs such as terbutaline, nifedipine [96] and atosiban [97], vasodilatators as sildenafil and nitroglycerine, and also antispasmodics [38] have all been proven to reduce dysmenorrhea but are associated with side effects such as tachycardia and headaches or, in the case of atisoban, is not being available in oral form.
Combined oral contraceptives (COC) inhibit gonadal estrogen, which suppresses ovarian activity. This leads to a limited endometrial growth and reduction of the amount of endometrial tissue available for PG and LT production as well as a reduction of estrogen-induced production of PGs reducing inflammation associated with dysmenorrhea and endometriosis [13,98,99]. Progestins create a hypo-estrogenic environment with atrophic endometrium as well as exerting an antiangiogenic and anti-inflammatory effect [100]. A Cochrane review from 2009 [99] suggests there was low evidence that COC would reduce dysmenorrhea, but since the studies in that review were made the level of hormones in the COC have changed and the long-cycle regime has been initiated.

A recent Cochrane report (2018) regarding the treatment of EAPP with COC concludes that there is insufficient evidence to make a judgment on the effectiveness of COC compared to other medical treatments or compared to placebo [101], only three trials were suitable for analysis of which two were at high risk for bias. Suggesting more high-quality trials are needed. The same conclusion is drawn in the report regarding NSAID and EAPP which included two studies [102]. The Cochrane review for Progestins, including 16 studies, shows that 100 mg/day medroxyprogesterone acetate (MPA) is a more effective analgesic than placebo but burdened with side effects [103].

Clinical guidelines [89,90,104] and a recent review of guidelines [105] suggest the use of COC and progestins for dysmenorrhea and endometriosis-associated pain as empirical treatment. Levonorgestrel releasing IUS has shown to be efficient in reducing dysmenorrhea post-surgery in women with endometriosis [106], reduce the size of recto-vaginal endometriotic lesions and reduce the level of dysmenorrhea and dyspareunia [107].

Estrogen suppression is not effective in all patients, which could be related to endogenous estradiol production within the endometriotic lesions. There is also relative progesterone resistance within endometriotic lesions [108], causing progestins failing to create a hypo estrogen environment [76].

GnRH (Gonadotropin-releasing hormone) agonists can be taken as injection or nasal spray, the effect is achieved through inhibiting the pituitary-gonadal axis resulting in hypoestrogenism with amenorrhea [109] and needs to be combined with add-back therapy to minimize bone density loss and hypo-estrogenic side effects [110]. The newest hormonal therapy available is GnRH-antagonist which is an oral treatment without the initial flare-up caused by the GnRH-agonists but with the same side effects e.g. hot flushes and bone density loss [111].

These hormonal treatments are all affecting endometriosis by temporarily inhibiting estrogen and the recurrence rate after the cessation of therapy is high. They are furthermore related to side-effects which in many cases are not well tolerated by the patients.

Aromatase inhibitors, immunomodulators, selective progesterone receptor modulators and histone deacetylase inhibitors show promising effect but there is not yet enough evidence for inclusion in routine clinical practice [98].

Surgery with excision of endometriotic lesions can be an effective treatment option for pain as well as for infertility but is associated with a high rate of recurrence [51,112]. There are cases of bowel obstruction or hydronephrosis due to deep infiltrating endometriosis, where surgery is the only option.

2.4 MELATONIN

2.4.1 Synthesis and metabolism

Melatonin is a hormone regulating the circadian rhythm, synthesized from serotonin mainly in the pineal gland in the brain, and secreted into the blood as well as into the cerebrospinal fluid [113]. The synthesis is synchronized to the light/dark cycle by photosensitive ganglion cells in the retina of the eye [114]. The synthesis is blocked by light at night, especially blue light. Secretion reaches peak levels at 02-04 am at night [115,116]. The effect of melatonin is mediated through two receptors, MT1 and MT2 [117] but also thorough receptor independent pathways [118].

Extra-pineal melatonin has been detected in all organs which have been examined [119]. Melatonin also seems to be synthesized from serotonin locally, the levels of melatonin in the extra-pineal locations are much higher than in plasma and have no day-night variations[113].

The circulating melatonin has a half-life of 30 min, with most of its metabolism occurring in the liver via cytochrome P450-mediated oxygenation, mainly through CYP1A2, then excreted in urine [120]. An inverse relationship between age and melatonin has been reported. Women seem to have a higher melatonin level than men [121].

There are inconsistent results regarding levels of melatonin during the menstrual cycle. Some studies have shown higher levels during the luteal phase [122,123] whereas other studies showed no change in the level of melatonin [124,125]. An elevated level in women with combined oral COC [125] and after GnRH-treatment [126] has been observed indicating a negative correlation between serum melatonin and serum estrogen (low estrogen – high melatonin). Women with hypothalamic amenorrhea had higher levels of melatonin compared with menstruating women [124,126].

The metabolism is affected by smoking [127] [128](reduced Cmax), food intake (recent food intake was associated with higher Cmax in a small study) [129], caffein (higher Cmax) and [127]certain drugs such as fluvoxamine by interacting with CYP1A2 (high Cmax) [130].

2.4.2 Analgesic effect

Animal studies conclude that melatonin has an analgesic effect for electrically, thermally, neuropathically, mechanically, chemically induced pain and also for inflammatory pain [131]. Human studies have shown analgesic effects of exogen melatonin in surgical patients [132,133] in procedural pain [134], but also in patients with chronic pain such as fibromyalgia [135,136].

In an RCT on humans 0.05 mg/kg/day, 0.15 mg/kg/day and 0.25 mg/kg/day melatonin or placebo were given to subjects submitted to pressure and heat pain stimuli. The results indicate that melatonin exerts a dose-dependent antinociceptive activity [137].

The analgesic effects of melatonin are not fully understood and have been attributed to its anti-oxidative properties [138], but it is now evident that naloxone inhibits the antinociceptive effect of melatonin suggesting the involvement of the opioid system, perhaps via melatonin receptors present in the spinal cord and in the brain [139]. Beta-endorphins, GABA (Gamma-aminobutyric acid) receptor and the nitric oxide (NO) arginine pathway have also been suggested to be involved [120,140].

2.4.3 Anti-oxidative effect

Melatonin is a well-documented scavenger of free radicals. The anti-oxidative effect is directly related to its concentration. At higher concentrations, there are more molecules of the antioxidant available to quench free radicals thereby lowering oxidative damage [141]. It also has the ability to stimulate antioxidant enzymes in different tissues [114]. Many chronic diseases have been associated with oxidative stress, but no success has been seen with anti-oxidative treatment. Stipulated reasons are lack of causal relationship or that concentrations at target are too low [80,113].

2.4.4 Melatonin and dysmenorrhea

A small study compared the analgesic effect of melatonin compared with meloxicam (NSAID) in women with moderate dysmenorrhea, no difference was seen between the groups [142], suggesting the analgesic effect of melatonin is comparable with that of meloxicam.

2.4.5 Melatonin and endometriosis

Mosher et al have shown that melatonin receptors are present in the human endometriotic glands and that melatonin inhibits the estrogen-driven proliferation of endometriotic cells [143]. The mechanism by which melatonin affects the endometrium and endometriotic tissue is still unknown.

Endometriosis has showed aberrant traits of the epithelial-mesenchymal transition (EMT) in increased rate of cellular migration, invasion properties and increased resistance to apoptosis. Melatonin inhibited the17β-estradiol-induced migration, invasion and epithelial-mesenchymal transition [144].

Animal studies on rodents have shown that melatonin decreased the size of endometriosis implants, increased the levels of antioxidant and antiangiogenic markers [145-147] and

increased apoptosis [148] in the endometriotic lesions. Another animal study with endometriotic implants comparing the effect of melatonin with aromatase inhibitor letrozol showed reduction of the size of the implants and a lesser extent of recurrence of the endometriotic lesions in the melatonin group after cessation of treatment [149].
Schwertner et al conducted a double blinded placebo controlled randomized controlled trial (RCT) assessing the analgesic effect of 10 mg melatonin given daily for eight weeks for AEPP. The results showed a statistically significant effect on reduction of VAS for AEPP, dyspareunia, dysuria, dyschezia and reduction of analgesic doses in the melatonin group as well as a reduction in s-BDNF (brain-derived neurotrophic factor) which is a mediator and a central modulator of pain [150].

2.4.6 Other effects

A recent study on fibromyalgia shows that melatonin has a dose-dependent effect on anxiety and quality of life [151]. A review showed melatonin to have similar anxyiolytic effect as midazolame, with less side-effects [152]. A meta-analysis showed 9 minutes reduction of sleep onset in secondary insomnia i.e. jet lag and shift work when given melatonin [153]. The antiestrogenic effect of melatonin is not completely known and has been studied in cancer research [154] as well as its immune modulating effects [155].

2.4.7 Safety

Melatonin is considered a safe drug. In a placebo-controlled toxicology assessment of 10 mg melatonin daily, no difference in adverse effects were noted between the groups [156]. Doses as high as 300 mg daily have been given long term, 2 years, without adverse effects in patients with ALS. Melatonin levels in plasma after 2 months did not show any signs of accumulation or altered metabolism [157]. It has been discussed that the organism might adjust itself to a new, higher, level of melatonin oscillations [114].
Melatonin is sold over the counter in many countries as a dietary supplement for inducing sleep. A Canadian study has shown that 71% out of the 30 tested supplements did not contain the labeled dose. Concentrations varied from -83% to +478%, and 26 % contained non-declared serotonin [158]. The variations in quality and actual concentrations affects the general attitude towards melatonin since most of its users buy it over the counter. The doses, and consequently, the clinical effects may vary.

3 RESEARCH AIMS

The overall aim was to assess how many young women in Stockholm suffer from dysmenorrhea, and to see if melatonin could be a new treatment option for them and for women with endometriosis-induced pelvic pain.

Study I – To assess the prevalence of dysmenorrhea in Stockholm, how it is managed and what implications it may have in the life of young women

Study II – To investigate if 10 mg melatonin daily could reduce the level of dysmenorrhea, the use of analgesics used for dysmenorrhea and to assess its tolerability

Study III – To investigate if 20 mg melatonin daily could reduce the level of endometriosis-associated pain, the use of analgesics, if it could improve quality of life and to assess its tolerability.

4 MATERIALS AND METHODS

4.1 SUMMARY OF STUDY DESIGNS IN THIS THESIS

Study	Study design	Population	Intervention	Comparison	Outcome	Time
I. Prevalence and impact of dysmenorrhea among Swedish adolescents	Population-based cross-sectional study	Girls born in the year 2000 (16-17 years old), living in Stockholm	NA	NA	Prevalence of dysmenorrhea	Cross-sectional
II. Adjuvant use of melatonin for pain management in dysmenorrhea - a randomized double-blinded, placebo-controlled trial	Randomized double-blinded, placebo-controlled trial	Adult women with severe dysmenorrhea	10 mg melatonin	Placebo	Reduction af pain due to dysmenorrhea	3 menstrual cycles
III. Adjuvant use of melatonin for pain management in endometriosis - a randomized double-blinded, placebo-controlled trial	Randomized double-blinded, placebo-controlled trial	Adult women with endometriosis-associated pain	20 mg melatonin	Placebo	Reduction of endometriosis-associated pain	3 menstrual cycles/ 3 months

Table 1. Overview of the studies in this thesis summarized according to the PICOT [159] format.

4.2 STUDY I

4.2.1 Study population and recruitment

All women born in the year 2000 and registered to be living in the municipality of Stockholm (n = 3998) were invited to participate in the study through a letter in an anonymous envelope. Information about the study and login details were included as well as information regarding anonymity. The login could only be used once. Two reminders were sent by mail. The survey was open for 6 weeks. Social media, Facebook and Instagram, were used to promote participation.

The survey was administered by SIFO-KANTAR (Swedish Institute for Opinion Surveys), an independent, non-biased Swedish company that conducts consumer research and testing (www.kantarsifo.se). SIFO is a subsidiary of Kantar (www.tnsglobal.com), which is part of the WPP Group plc (www.wpp.com).

4.2.2 Questionnaire

We created the questionnaire, which was slightly modified by SIFO-KANTAR for clarity to the participants. Answering one question unlocked the next, with some answers leading to follow-up questions. For those who had not yet started with their menstruation the survey only consisted of two questions: age and if they had had their first period yet. Those who

reported no dysmenorrhea or “don’t know” finished after 3 questions. The maximum number of questions was 58.

Questions included level of dysmenorrhea on a numeric rating scale (0-10), which analgesics they used and how they used them. Questions regarding dysuria, dyschezia and dyspareunia were included as well as what effects the pain had on their daily lives.

4.2.3 Statistical analysis

Descriptive statistics were used to present the findings in proportions, with 95% CI-intervals.

4.3 STUDY II

4.3.1 Study population

Study participants were all living in the Stockholm area and recruited through posters in gynecological outpatient clinics and youth clinics as well as through social media. The main inclusion criterium was a reported level of dysmenorrhea ≥ 7 on NRS.

Inclusion	**Exclusion**
≥18 years old	Smoker
Willingness to keep a pain diary for the study period of three months	Pregnant
Good general health	Fluvoxamine treatment
Swedish speaking	Change in medical therapy during the last 3 months
Regular periods	Diagnosed endometriosis
	Hormonal contraceptive altering menstruation
	History of or current disease of liver or kidney

Table 2. Criteria of inclusion and exclusion of study II

4.3.2 Study design

The duration of the study was three menstrual cycles. The first was a screening cycle followed by two treatment cycles during which the study drug was ingested for 7 days at bedtime, starting on the evening of the first day of menstruation. There were four visits at the Women’s health research center at Södersjukhuset.

After a pre-screening on the phone by the research nurse, a screening visit with one of the two doctors working with the study was scheduled. During the screening visit the potential participant was informed about the study, orally and in writing and signed an informed consent. A pregnancy test was taken and an assessment for signs of endometriosis was made with vaginal ultrasound. The participant was instructed how to register her symptoms in an online survey sent to their email daily, through RedCap [160] starting on the first day of menstruation.

Eligible participants were included and randomized to a treatment group and given the study drug on visit 2, day 1-4 in the screening menstrual cycle, providing the inclusion criteria had been met (some had ≥ 7 on NRS day 1). They completed a questionnaire assessing sleep (ISI – insomnia severity index) and a cognition survey, administered by CANTAB (Cambridge Neuropsychological Test Automated Battery) [161] assessing motor screening tasks, reaction time, rapid visual processing, paired associates learning, and spatial working memory, was performed on a tablet computer.

Visit 3 took place on day 1-4 in the second treatment cycle during which the participants took the sleep and cognition surveys again.

The participants came back for visit 4 after the second treatment cycle to return any remaining drugs and evaluate the tolerability and acceptance of the study drug.

Visit 1 was conducted by one of the two doctors, visit 2-4 was conducted by one of the two research nurses or one of the doctors.

The daily, online questionnaire assessed level of dysmenorrhea, amount of analgesics, amount of bleeding according to PBAC - pictorial blood loss assessment chart and potential adverse effect.

The study drug consisted of 10 mg melatonin or placebo, each dose identical and dispersed in two capsules of 5 mg melatonin or placebo.

4.3.3 Questionnaires

All questionnaires were administered through RedCap and sent daily to the participants by email.

NRS- numeric rating scale a subjective measure of pain intensity [162] was registered daily.

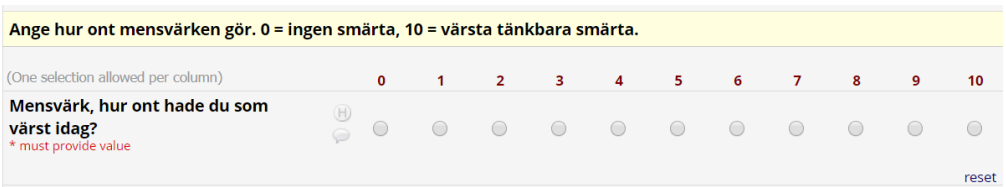

Figure 3. NRS – numeric rating scale as seen in the questionnaire

ISI - Insomnia severity index is a questionnaire with 5 questions assessing sleep. Total score range from 0 to 28, ≥15 signifies clinical insomnia [163,164].

CANTAB – cognition test assessing attention, psycho-motor speed and memory through tests performed on a computer tablet [161].

PBAC- Pictorial blood loss assessment chart is a subjective assessment of the volume of blood loss through menstruation [165]. Total score >100 is considered as heavy menstrual bleeding [166].

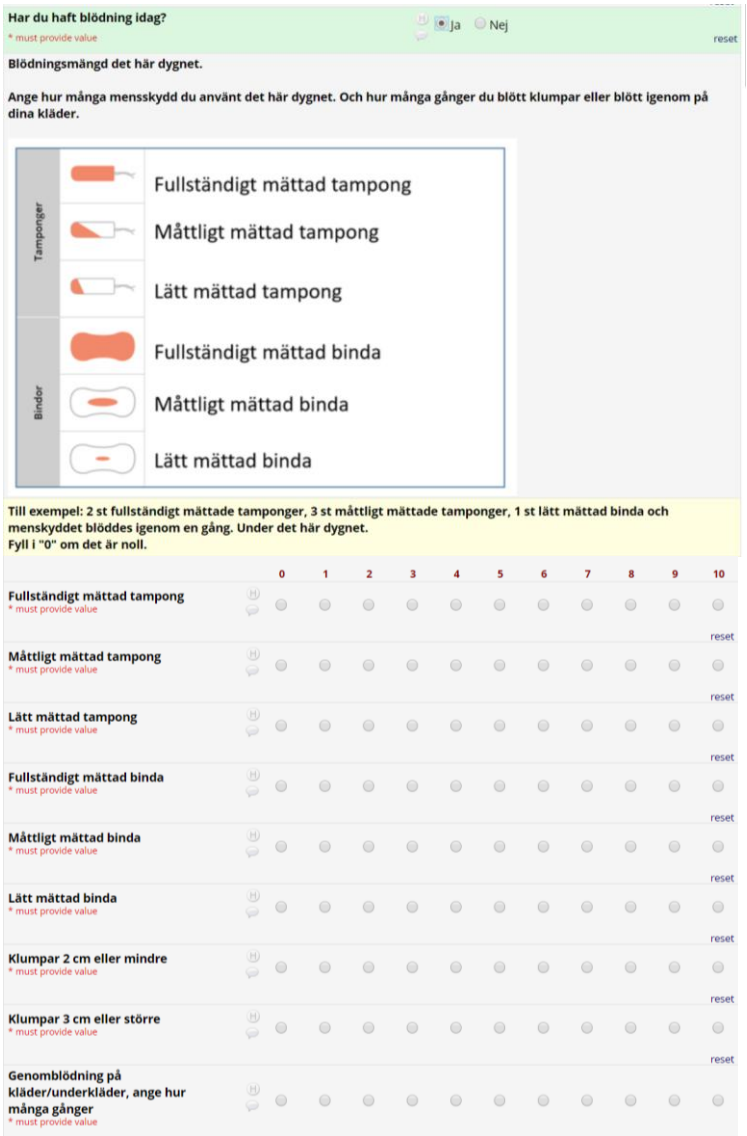

Figure 4. PBAC - Pictorial blood loss assessment chart as seen in the questionnaire

4.4 STUDY III

4.4.1 Study population

Study participants were recruited through posters in gynecological outpatient clinics and youth clinics as well as through social media. Main inclusion criteria was a reported level of endometriosis-associated pain ≥ 7 on the NRS during menstruation or a mean of ≥ 4 for 7 days during the last 6 months. Due to difficulty recruiting we lowered the mean NRS to

≥ 3 and also to include participants with hormonal therapy and amenorrhea.

Inclusion	Exclusion
≥18 years old	Smoker
Willingness to keep a pain diary for the study period of three months	Pregnant
Good general health	Fluvoxamine treatment
Swedish speaking	Change in medical therapy during the last 3 months
Endometriosis*	Regular opioid treatment for pain
	History of or current disease of liver or kidney

Table 3. Criteria of inclusion and exclusion of study III. ***** Diagnosed through laparoscopy, ultrasound or MRI.

4.4.2 Study design

The duration of the study was three menstrual cycles/months. One menstrual cycle/month of screening followed by two cycles/months of treatment. Due to the covid-19 pandemic the study was made entirely remote after having screened 24 and included 16 of them. Screening was initially made by phone and later through an online survey. The first visit was with a doctor, the participant received information orally and in writing and signed an informed consent form. A urine pregnancy-test was done to exclude pregnancy.

The daily online questionnaire included level of EAPP, dysuria, dyschezia and dyspareunia, PBAC and amount of analgesics. On day 21 of the first and last cycle the participants received a survey assessing sleep (ISI), Endometriosis health profile (EHP-30) and pain catastrophizing scale (PCS).

By the end of the screening cycle, if eligibility was met, inclusion and randomization was made during a visit or a video call, and the study drugs were sent by registered mail or delivered by the investigator. During the pandemic the inclusion visit was replaced with a video call during which an initial verbal informed consent was obtained.

A pregnancy test and a pre-stamped envelope to return the signed informed consent form was included in the package. Tolerability was assessed with an online survey after the study.

The study drug consisted of 20 mg melatonin or placebo, each dose identical and dispersed in four capsules of 5 mg melatonin or placebo.

4.4.3 Questionnaires

NRS and ISI, same as in study II

EHP-30 – Endometriosis health profile consists of 30 questions assessing symptoms in women with endometriosis. There are 5 sections: pain, control and powerlessness, emotional well-being, social support and self-image. Higher scores indicate increased severity of symptoms [167,168].

PCS – Pain catastrophizing scale measures the degree of pain catastrophizing of the participant by measuring elements of helplessness and pessimism in relation to the ability to deal with the pain experience. Consisting of 13 questions, with a maximum score of 52. A high score on the PCS reflects a high degree of pain catastrophizing [169,170].

4.5 RANDOMIZATION STUDY II & III

The study drugs were manufactured for the trials by APL, Stockholm, Sweden, in consecutively numbered drug containers. Randomization was made by the manufacturer of the study drug, by blocks of 4. The randomization key of each study was retrieved and opened after the last participant had completed their respective study, thus assuring that the blinding was maintained during the treatment phase of the trials.

4.6 POWER CALCULATION AND STATISTICAL ANALYSIS STUDY II & III

To detect a clinically significant reduction of NRS of 1.3 units [171] with a power of 80% and a 2-sided alpha value of 0.05, 15 participants in each group were needed. We included 20 participants in each group, in total 40 participants, to compensate for potential dropouts.

Independent t-tests were used to compare baseline characteristics as well as number of days of pain, days with analgesics and the scores for CANTAB, ISI, EHP and PCS.

Mixed model was used to compare treatment effects. The best fitting model for study II was obtained with an unstructured model for outcome 1, with fixed effect and fixed intercepts. AR(1) showed the best fit for outcome 2, with fixed effects and random intercept. The best fitting model for all outcomes in study III was covariance structure AR(1) with random intercept, without random slope.

Interactions between time and treatment was tested to study if the outcomes differed between the groups at different timepoints. Interaction between weight and treatment was tested in both studies. In study III interaction between hormonal therapy and treatment was tested. The first day was excluded of inference since the study drug was ingested at bedtime and that day was considered un-treated.

Acceptability was compared with Fisher's exact test.

A two-tailed p-value < 0.05 was considered to indicate statistical significance. SPSS version 26 (SPSS, Chicago, IL) was used for data analyses.

Registration number at Clincaltrials.gov was NCT037827404.

5 RESULTS

5.1 STUDY I

Study I examined the prevalence and impact of dysmenorrhea amongst young women born in the year 2000 residing in the municipality of Stockholm. The main results were:

- There was a 45% (1785/3998) response rate. Mean age of the respondents was 16.2 years. Mean age for menarche was 12.4 years
- 89% (1580/1785) reported to suffer from dysmenorrhea
- 25% had mild dysmenorrhea (NRS 1-4), 39% had moderate (NRS 5-7) and 36% had severe (NRS 8-10)
- Fatigue was reported by 83% (1314/1580) and headache by 82% (1296/1580) These symptoms were more common in the group with severe dysmenorrhea

	Dysmenorrhea	Mild		Moderate		Severe		Total	
		N	%	N	%	N	%	N	%
Blood clots	Every month	92	6%	183	11%	368	23%	643	40%
	Few times per year	118	7%	232	14%	303	19%	653	41%
	Never	68	4%	115	7%	127	8%	310	19%
The need of double protection	Every month	39	2%	82	5%	173	11%	294	18%
	Few times per year	57	4%	109	7%	155	10%	321	20%
	Never	182	11%	339	21%	470	29%	991	62%
Bleeding through clothes	Every month	40	2%	80	5%	179	11%	299	19%
	Few times per year	134	8%	276	17%	424	26%	834	52%
	Never	104	6%	174	11%	195	12%	473	29%

Table 4. Symptoms related to menstruation, table not presented in the article

- 59% (930/1580) reported having cancelled social activities due to dysmenorrhea
- Absenteeism from school every month due to dysmenorrhea was reported by 14 % (228/1580), by the majority of which suffered from severe dysmenorrhea
- Healthcare facilities including school nurse had been visited by 33 % (525/1580) Docotor had been consulted by 7% (117/1580)
- Hormonal therapy prescribed dysmenorrhea was used by 10% (157/1580) and for another 10% (156/1580) for contraception.
- A general sub-optimal use of analgesics was reported
- Symptomatologic signs of endometriosis were presented by 6% (severe dysmenorrhea in spite of using hormonal therapy and non-sufficient effect of analgesics)

Analysis not shown in the article:

- Those with early menarche (11 years or younger) had a 1.4 times higher risk to have severe dysmenorrhea. (95% CI 1.2-1.6)

5.2 STUDY II

Study II examined if 10 mg melatonin had any clinically significant analgesic effect, pre-specified to a reduction of 1.3 units on the NRS, in women with dysmenorrhea in comparison with placebo. 20 women were included in each treatment arm.

The main findings were:

- No clinically significant differences between the randomized treatment groups at baseline when analyzed with independent t-test

	Placebo		Melatonin		
	n	Mean (SD)	n	Mean (SD)	p-value
Age	20	28.5 (7.2)	20	27.0 (5.2)	.45
Weight, in kg	20	72.8 (16.7)	19	68.8 (13.1)	.42
Number of pregnancies	18	0.8 (1.2)	20	0.5 (1.0)	.37
Pain, mean	19	3.6 (1.0)	20	4.4(1.7)	.10
Days of pain	20	4.4 (1.2)	20	4.8 (1.7)	.40
Total amount of analgesics in mg	20	4695.0 (3880.4)	20	4887.5(5715.1)	.90
Days of bleeding	20	4.8 (1.0)	20	5.4 (1.1)	.10
Total PBAC	20	120.2 (59.7)	20	125.6 (122.2)	.86

Table 5. Baseline characterstics. One participant in the placebo group failed to report the level of dysmenorrhea for every day in the baseline cycle.

- In the melatonin group 19 participants fulfilled the study, 1 discontinued due to initiating another medical treatment. In the placebo group 18 participants fulfilled the study, 2 were lost to follow up
- Primary outcome - No clinically significant difference was seen between the groups in the level of dysmenorrhea. Mean level of dysmenorrhea 0.73 units lower in the placebo group during the treatment cycles (p= 0.02)
- Secondary outcomes - No significant differences between the groups in the level of dysuria, dyschezia and amount of analgesics

Outcomes	Treatment	n	Adjusted mean (SD)	Adjusted mean difference	95% Confidence intervals	p-value
Pain NRS	Placebo	18	2.5 (2.9)	-.7	-1.3 to -.2	.02
	Melatonin	19	3.2 (3.37)			
Amount of analgesics (mg)	Placebo	18	464.0 (986.2)	-115.3	-497.6 - 267.0	.51
	Melatonin	19	579.3 (1192.0)			
Days with dysmenorrhea*	Placebo	18	3.9 (1.2)	-.8	-1.4 to -.1	.02
	Melatonin	19	4.7 (1.5)			
Days with bleeding*	Placebo	18	4.8 (1.0)	-.2	-.7 - .3	.33
	Melatonin	19	5.0 (1.2)			
PBAC*	Placebo	18	129.8 (64.9)	-5.8	-57.8 - 46.3	.82
	Melatonin	19	135.6 (143.4)			

Table 6. Outcomes in means, of the two seven-day cycles. (ITT). Analyzed with mixed model analysis and *with unpaired t-test.

Last cycle, day 2-4	Placebo N=15 Mean value (SD)	Melatonin N=17 Mean value (SD)	Adjusted mean difference (95 CI)	p-value
Motor screening task, mean latency, milliseconds (MOTL)	743.9 (306.2)	701.6 (203.1)	42.4 (-143.1-227.9)	.64
Paired associates learning, number of times the incorrect box was chosen for a stimulus (PALTEA)	4.9 (5.0)	9.1 (7.7)	-4.1 (-8.9-0.6)	.09
Reaction time task, mean reaction time, milliseconds (RTIFMDRT)	346.5 (36.1)	352.7 (35.7)	-6.2 (-32.1-19.8)	.63
Rapid visual information processing, sensitivity to detecting target sequences (RVPA)	.9 (.1)	.9 (.1)	0.0 (-0.1-0.0)	.74
Spatial working memory, strategy for finding tokens (SWMS)	5.5 (3.6)	5.9 (2.9)	-0.4 (-2.7-2.0)	.77

Table 7. CANTAB. Table not presented in the article. Data is missing from 2 participants in the placebo group and 1 in the melatonin group, the participants could not come to the visit. Two participants, one in each group, took the CANTAB-test on day 1 and were excluded from the analysis due to not yet having taken the study drug. No statistical difference was seen with or without those 2 participants. Analyzed with unpaired t-test.

- No serious adverse effects were reported. Abdominal pain and slight vertigo was reported respectively by two participants in the placebo group. Heartburn together with abdominal pain was reported by one participant in each group. Headache and

loss of concentration was reported by one participant in the melatonin group. None of these participants discontinued the treatment

Analysis not presented in the article

- Some participants had only taken the study drug for one night and some for four nights when assessment of sleep was made. No significant difference was seen between the groups

Treatment group	n	Mean (SD)	Mean difference	Confidence Interval 95%	p-value
Placebo	16	10.9 (6.7)	-1.2	-5.5 - 3.1	0.58
Melatonin	18	12.1 (5.6)			

Table 8. Insomnia sleep index excluding one participant in each group who took the test the first day of the cycle meaning they had not yet taken the study drug. Data is missing from one in the placebo group. Analyzed with unpaired t-test.

- Within group analysis, mean dysmenorrhea

Treatment group		N	Mean (SD)	Mean difference	p-value
Placebo	Cycle 1	18	3.8 (1.3)		
	Cycle 3	18	3.3 (1.4)	.5	.19
Melatonin	Cycle 1	19	4.6 (1.7)		
	Cycle 3	19	3.9 (1.8)	.7	.04

Table 9. Paired t-test of mean pain showed a higher reduction in mean pain in the melatonin group.

- Per protocol analysis, mean dysmenorrhea

Treatment group	n	Adjusted mean (SD)	Adjusted mean difference	Confidence Interval 95%	p-value
Placebo	16	2.6 (2.8)	0.5	-1.0 to -.1	0.09
Melatonin	16	3.1 (3.4)			

Table 10. Per protocol analysis. Mixed model analysis of variance. In the placebo group 1 participant had pain scores lower than the inclusion criterium and 1 had taken less than 80% of the study drug. In the melatonin group 1 participant had irregular bleeding, and 2 had taken less than 80% of the study drug.

5.3 STUDY III

Study III examined if 20 mg melatonin had any clinically significant analgesic effect, pre-specified to a reduction of 1.3 units on the NRS, in women with endometriosis-associated pain in comparison with placebo. 20 women were included in each treatment arm.

The main findings were:

Mean (SD)	**Placebo n= 20**	**Melatonin n= 20**	**p-value**
Age	34.2 (7.7)	35.9 (6.6)	.46
Length, cm	168.2 (6.0)	167.2 (6.3)	.61
Weight, kg	68.8 (6.8)	72.2 (15.5)	.38
Number of pregnancies	1.5 (1.7)	1.2 (1.5)	.63
Number of deliveries	.7 (1.2)	.7 (1.0)	1.0
Number of miscarriages	.3 (.8)	.4 (.8)	.85
Contraceptives n (%)			.46
None	6 (30 %)	5 (25%)	
Condom	3 (15%)	7 (35%)	
Progestin pill (eg desogestrel)	1 (5%)	0	
Progestin- dienogest	1*	0	
Hormonal IUS, 52 mikgr LNG	4* (20%)	4 (20%)	
Hormonal IUS, 19.5 mikgr LNG	1 (5%)	0	
COCP	1 (5%)	0	
Sterilization	0	1 (5%)	
Missing data	4 (20%)	3 (15%)	
Use of hormonal therapy n (%)			.29
Without hormonal therapy	13 (65%)	16 (80%)	
Mean (SD)			
EAPP mean	3.6 (1.9)	2.9 (1.9)	.20
Analgesics in mg, mean	825.3 (981.1)	661.9 (776.7)	.56
Dysuria, mean	1.6 (1.8)	1.6 (2.1)	.95
Dyschezia, mean (n 20/19)	2.1 (2.1)	1.6 (2.0)	.40
Dyspareunia, mean (n 16/14)	2.1 (2.5)	.6 (.92)	.04
Total (SD)			
Number of days w EAPP	23.9 (7.2)	19.8 (8.9)	.12
Number of days w analgesics	12.2 (8.5)	10.8 (8.1)	.58
Mean (SD)			
Insomnia severity index	13.8 (6.1)	12.4 (6.0)	.47
EHP - pain	48.3 (20.0)	48.5 (22.6)	.97
EHP - control	61.9 (23.9)	60.2 (22.9)	.82
EHP - emo	48.1 (21.7)	49.2 (20.0)	.88
EHP - social	53.1 (21.5)	49.1 (28.3)	.61
EHP - self esteem	61.3 (27.9)	62.1 (21.4)	.92
Pain catastrophizing scale	25.3 (9.4)	27.6 (10.3)	.47

Table 11. Baseline characteristics. *One participant in the placebo group had both hormonal IUS and Dienogest. LNG = levonorgestrel.

- No significant differences between the randomized treatment groups at baseline when analyzed with independent t-test
- In the placebo group 16 participants fulfilled the study, 2 were lost to follow up, 2 discontinued. In the melatonin group 18 participants fulfilled the study, 1 was lost to follow up, 1 discontinued due to restless legs

- Primary outcome - No significant difference between the groups in the level of endometriosis associated pain

	Treatment group	n	Adjusted mean	Adjusted mean difference	Confidence Interval 95%	p-value
Endometriosis-associated pain	Placebo	16	3.2 (2.0)	.3	-.7 - 1.4	.52
	Melatonin	18	2.9 (1.9)			
Analgesics, mg	Placebo	16	505.6 (762.4)	-136.7	-571.7 - 298.3	.53
	Melatonin	18	642.2 (915.9)			
Dysuria	Placebo	16	1.2 (1.7)	.1	-1.0 - 1.1	.93
	Melatonin	17	1.1 (1.8)			
Dyschezia	Placebo	16	1.7 (2.0)	.6	-.5 - 1.7	.26
	Melatonin	17	1.1 (1.7)			
Dyspareunia	Placebo	12	1.1 (1.8)	.4	-.7 - 1.4	.50
	Melatonin	15	.7 (1.2)			

Table 12. Treatment effect on the outcomes during the study period, two menstrual cycles/months, analyzed with mixed model of variance.

- Secondary outcomes - No significant differences between the groups in the levels of dysuria, dyschezia and amount of analgesics in mg, nor in sleep (ISI), pain catastrophization (PCS) and quality of life (EHP-30)
- Adherence rate was high – No participant had lower adherence than 82%
- No unknown adverse effects were reported, one participant in the melatonin group experienced restless legs and discontinued. Suspected urticaria, diarreha for a few days and pain from known gallstones was reported by three different participants

Analysis not presented in the article

- It has been suggested that the pain during menstruation should be analyzed separated from the average pain in endometriosis [172]. There were no differences between the treatment groups when the week of menstruation separatly
- Subgroup analysis

12 participants had a mean value of EAPP ≥4 during the screening cycle, 5 were randomized to the melatonin group from which 1 discontinued. Seven were randomized to the placebo group, from which 2 discontinued. No difference was seen between the groups in the mixed model analyses of all outcomes in baseline or in the treatment cycles, nor in the independent t-test analysis of PCS, EHP-30 and ISI. Hormonal therapy was used by 42% (5 out of 12), compared to 21% (6 out of 28) of those with lower pain score

- Per protocol analysis, mean EAPP

Treatment group	n	Adjusted mean (SD)	Adjusted mean difference	Confidence Interval 95%	p-value
Placebo	15	3.2 (1.7)	.3	-1.0 - 1.6	.62
Melatonin	15	2.8 (1.8)			

Table 13. The per protocol analysis. Mixed model analysis of variance. One participant failed to report correctly. In the melatonin group I was wrongfully included and 1 had oligomenorrhea.

6 DISCUSSION

6.1 STUDY I

A cross-sectional study

6.1.1 Main findings and interpretation

Dysmenorrhea was reported by 89% (1580/1785) out of which 36% (574/1580) reported severe dysmenorrhea (NRS 8-10). 59% (930/1580) reported having cancelled social activities due to dysmenorrhea. Only a few 7% 116/1580) have consulted a doctor which leads us to suspect a normalization of, even disabling, dysmenorrhea.

The sub-optimal use of analgesics and level of monthly absenteeism (reported by 14% of the respondents) is similar to other studies. Factors associated with severe dysmenorrhea such as heavier menses and early age at menarche had higher representation in those with severe dysmenorrhea.

There is a high level of fatigue (83%) and headache (82%) which could be a sign of iron deficiency or anemia. The prevalence of iron-deficiency among adolescent girls has been shown to be 19-35% [173,174] (using different cut-offs), and 10% [174] for iron-deficiency anemia.

The disabling effects of dysmenorrhea could to a certain extent be alleviated with the proper use of analgesics and hormonal therapy. And those with insufficient effect of such treatment should be assessed for endometriosis or other pathologies. But for the normalization to cease awareness is key, by recognizing that absenteeism due to dysmenorrhea is not a physiological aspect of being female.

6.1.2 Methodological considerations and validity

Cross-sectional studies are observational studies collecting information at one point in time and the results are often presented with descriptive analysis. Analytical analysis can however also be made and associations between variables can be shown. There is a risk of reversed causality since the study design does not show if the outcome or the exposure came first. Since it is a one point in time measurement there is no temporal aspect of the data. However, if the exposure is considered stable in relation to the outcome even causal associations can be identified.

Age at menarche is a stable exposure in relation to dysmenorrhea meaning there is probably no reversed causality, but potential confounders need to be taken into consideration to make any inference on causality.

Systematic errors

The response rates in epidemiological studies in general have been falling the last years [175,176] one explanation being "survey fatigue" [177]. The response rate in study I is high compared with other surveys targeting the same age group during approximately the same time. SOM (Samhälle, Opinion, Media) Instituet had a 46% response rate 2017, amongst 16-19-year-olds, but with an incentive (a lottery ticket)[176] and "UngKAB15 – a survey on Knowledge, Attitudes and Behaviour" 2015-2016 had a response rate of 26% [178].

The response rate of 45% (1785/3998) could introduce *selection bias* as well as lower the representability. The high prevalence of dysmenorrhea could be due to *Neyman bias*, meaning that those with no menstrual problems chose not to respond, leading to an inflation of the observed prevalence. The invitation letter was neutral and disclosed that the study was about menstrual issues, not about dysmenorrhea specifically, to try and reduce selection bias. Two reminders were sent to augment the response rate.

We had no information about the 2418 (55%) non-responders. A sensitivity analysis was performed by assuming all non-responders were free of dysmenorrhea resulting in a hypothetic lowest possible prevalence of dysmenorrhea of 40% out of which 14% would suffer from severe dysmenorrhea and 6 % would be absent from school every month.

The study population poses a possible selection bias being a Swedish speaking urban population with access to computer, computer table or smart phone.

By not using a validated questionnaire we might have introduced *information bias* such as *misclassification bias*. At the time of the study initiation, no validated questionnaire for dysmenorrhea existed. A certain extent of recall bias can be present, which either underestimate or overestimate the results.

Any variable that could affect both exposure and outcome could be a *confounder*. Classic confounders are age and gender, which are taken care of by our study design including only females of the same age. Confounders can also be addressed in the analysis if the cross-sectional study had been analytical in addition to being descriptive. In the paper presenting study I only descriptive analysis was presented. In this thesis however, an inference on the association between early menarche and severe dysmenorrhea was made suggesting that those young women with menarche at the age of 11 years or younger had a 1.4 times higher risk to have severe dysmenorrhea. (95% CI 1.2-1.6). According to this DAG (Fig. 5) there were no confounders to adjust for. Had there had been any potential confounders, a multi-variable regression analysis could have been used.

.

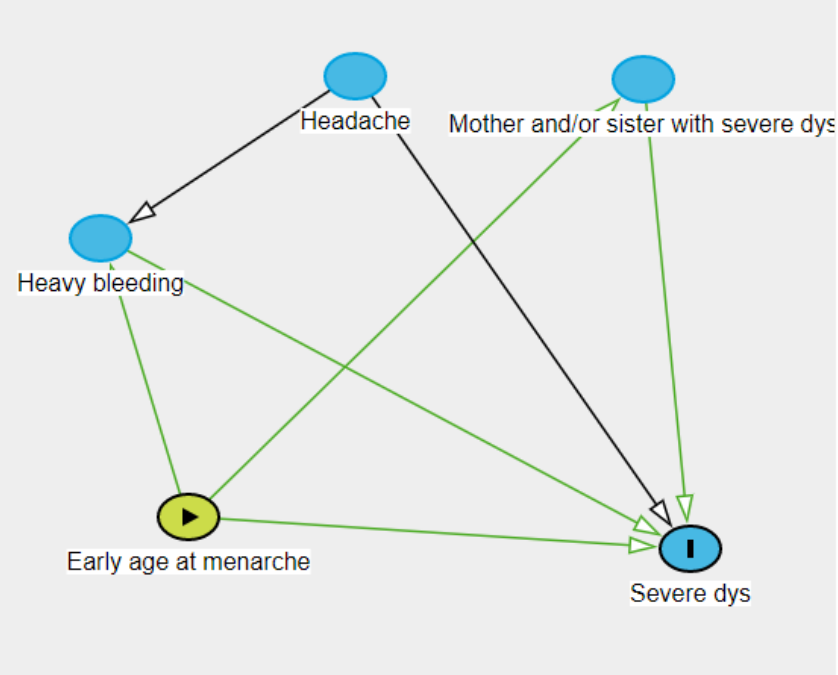

Figure 5. A direct acyclic graph (DAG) can be used to visualize potential causal pathways.

Validity

These systematic errors lower the internal validity of the study. The response rate of 45% affects the external validity. Mean age of menarche in the study was 12.4, 12 respondents were pre-menarche. The mean age of menarche in Sweden is 13 years [179]. Which suggests a potentially reduced representation and external validity, meaning the applicability to the general population is attenuated.

Random error

Random errors occur by chance, they usually decrease when the sample size is increased. They reflect the precision which is estimated by p-value or confidence intervals. Regarding early age at menarche for example: The risk ratio of 1.4 with 95 % CI 1.2-1.6 tells us that with 95% confidence the true value lies within that range, and because it does not contain the null-value (= 1) it indicates that is statistically significant.

6.1.3 Clinical and scientific context

There are several prevalence studies from different countries assessing dysmenorrhea and its impact. The only similar study made in Sweden was made in Gothenburg in 1982 and showed a prevalence of 72% ,15 % had severe dysmenorrhea and monthly absenteeism was reported by 8% in a study population consisting of 19-year-olds. In comparison things seem to have gotten worse with a prevalence of severe dysmenorrhea and absenteeism almost

twice as high some 35 years later. The use of oral contraceptives was higher in the previous study with 44% compared to 20% in our study.

In 1990 Sundell et al [19] made a follow-up study with the previously mentioned women in Gothenburg and stated that it was "surprising to note that a large number of women with dysmenorrhea still apparently suffer in silence, despite the availability of effective treatment". That was 30 years ago, and it seems that an even higher proportion of young women suffer now. The increasing lack of confidence in existing treatments is a worrying trend. There is a higher level of suspicion towards hormonal contraceptives in Sweden compared with other countries as well as a declining trend in the use of hormonal contraceptives [180].

6.2 STUDY II & III

Randomized, double-blinded, parallel, placebo-controlled trials. Both are longitudinal studies with repeated measures.

6.2.1 Main findings and interpretation

Study II The analysis of the primary outcome showed no clinically significant difference between the groups, there was however a statistically significant difference of 0.73 units lower pain scores in the placebo group. No statistically significant difference in the secondary outcomes i.e., intake of analgesics.

Ten mg of melatonin did not affect cognition in any measurable way which could be used as safety variable although we assessed it to see if a better pain management could improve cognition.

Study III The analysis of the primary outcome showed no clinically or statistically significant differences between the group. The pain score was 0.3 units lower in the melatonin group. No statistically significant difference in the secondary outcomes i.e., intake of analgesics.

6.2.2 Methodological considerations and validity

Systematic errors

No validated questionnaire specific for dysmenorrhea was used, which could introduce *information bias*. The NRS which is validated for acute pain was used, daily assessments were made to reduce recall bias. In **study III** we combined NRS with validated questionnaires for sleep (ISI) and for indicators of chronic pain and quality of life (EHP-30) and pain catastrophizing scale (PCS).

Double blinding was assured to reduce subject error and observer error. There seems to be *participant expectation bias* probably due to highlighting the effect of the study drug during recruitment which could explain the great improvements in the placebo group [181].
We did not provide participant training of the NRS scale, which is highly subjective. But we did provide an anchor to the highest value as "the worst pain ever experienced".
Misclassification bias could be present in **study III** as the diagnosis of endometriosis was not verified with e.g. medical records, which could underestimate the effect if the experienced pain was in fact related to something else.
The level of *confounding* was reduced by the most powerful method - randomization. But there could still be unknown confounders. Adjustment for weight showed no difference on the outcome in **study II and III**. In **study III** adjustment for hormonal treatment was made with no difference on the outcome. Participants with well-treated depression were included, who are generally excluded in chronic pain trials, 2 participants in the melatonin group were on antidepressant and 1 in the placebo group who theoretically could respond differently to pain treatment [182], excluding those participants resulted in a minimal change on the outcome with a difference of 0.4 units on NRS in favor to melatonin (p=0.52). We did not evaluate intake of food or caffeine which could interfere with the metabolism of melatonin, we did not measure levels of melatonin in serum which might have provided useful information.
There can be bias in the analysis ITT (intention to treat) vs PP (per protocol) [183], ITT tends to show an underestimation of treatment effect while PP is suggested to show an inflated treatment effect as it only includes those who fulfilled the trial and adhered to the protocol. However, no clinically or statistically significant difference between the treatment groups was seen in the PP analysis in **study II** nor in **study III** (Table 10 and Table 13).

Random error

The randomization effect is measured with a p-value to make sure there is no difference between the allocated groups at baseline before the treatment is initiated. In the analysis the p-value is used to make sure the difference in outcome did not occur by chance.
The difference of the main outcome in **study II** had statistically significant p-value at 0.02 meaning that the null hypothesis - no difference between the groups- is rejected because there is less than a 5% probability that the null hypothesis is correct (and the results are random) as we had set our threshold of significance (type I error rate) to 0.05.
Was there a type 1 error or did melatonin cause a statistically significant higher level of dysmenorrhea? There was a slightly larger reduction of NRS in the melatonin group (0.70

vs 0.55-unit, table 7) in a within group analysis (paired t-test) which leads us to believe that melatonin did not cause more dysmenorrhea. The standard deviation at baseline was larger than we estimated meaning the study could be underpowered. A larger study would reduce random error but would most likely not prove positive results in regards of clinical efficacy of 10 mg melatonin.

Wide confidence intervals and high p-values were observed for the secondary outcome intake of analgesics in **study II** & **III**, which probably is explained by the small sample sizes as well as there not being any difference between the groups.

Validity

External validity in RCTs are in general low due to strict inclusion criteria. In **study III** we widened the inclusion criteria when including those with hormonal treatment augmenting external validity but to the price of lowering internal validity by introducing possible confounders. The use of other analgesics reduces the assay sensitivity [184] but is more ethical and, for many participants, a condition for agreeing to participate, which is why intake of analgesics is an important secondary outcome. An average of NRS ≥ 4 is often used as inclusion criterium in chronic pain trials to avoid "floor effect" [185], it is uncommon for the mean pain intensity to fall below a mean of 3 or 4 [186] in chronic pain trials. Due to recruiting difficulties we needed to lower the score to NRS ≥ 3, which may have reduced the possibility to show any further reduction of pain.

Power calculation

There are different ways to calculate the sample size which correlates to power of the study. We based the sample size for **study II** and **III** on the similar study by Schwertner [150] to detect a difference of 1,3 units [171] on the numeric rating scale.

Schwertners study population had a standard deviation of 2.1 and 2.6 of the mean outcome in the two treatment groups respectively, in the baseline characteristics. Other ways to calculate the sample size would have been to use the mean SD of the previous study of 2.35 which would require a total of 106 participants to detect a difference of 1,3 units between the groups with a power of 80% and a 2-sided alpha value of 0.05. (i.e. an 80% chance to find a difference of mean NRS of 1.3 units).

Or we could have calculated an estimation of SD = range of NRS/6 or 4= 1.67 or 2.5 [187].

In **study III** the difference of the main outcome between the groups was 0.3 (95% CI -.7 – 1.4, p= 0.52). We prespecified that a minimum difference of 1.3 units would be clinically significant. Since that number lies within the range of the 95% CI, it suggests that the study

may be underpowered and that there is a type II error, making the study results inconclusive, rather than negative. A larger study population may show statistically significant results but maybe not clinically significant given the small effect of 0.3 units shown in **study III**.

6.2.3 Clinical and scientific context

At the time of the study initiation one other small study has evaluated the effect of melatonin on dysmenorrhea, this study comparing 3 mg melatonin with meloxicam (a non-steroid anti-inflammatory drug) with no difference between the groups [142] suggesting the analgesic effect of melatonin was as good as the effect of NSAID.

Study II could not show that 10 mg melatonin at bedtime was superior to placebo in treating dysmenorrhea. Given the rapid onset of dysmenorrhea and the short half-life of melatonin there was perhaps no possibility to have a direct analgesic effect with the chosen regime. Given the inflammatory aspect of dysmenorrhea with the oxidative stress, perhaps an anti-inflammatory and anti-oxidative effect would have been achieved if we had given melatonin in the pre-menstrual phase (Fig. 2). Or perhaps there would be an analgesic effect if melatonin was taken at the onset of pain, and then repeatedly. In most pain studies the melatonin is given at bedtime to mimic the endogenous cycle and to benefit from the potential sedative effect. There are however conflicting results regarding the sedative effect where it has been shown that no difference in reaction time was seen between 10 and 100 mg melatonin and placebo respectively [188] and no sedative effect was registered when 3 mg of melatonin was given in the mornings as part of a twice daily regime to menopausal women [189].

The pain experience is a complex interplay of physical, psychological, environmental, and social variables [190,191]. In chronic pain, pain cognition refers to the psychological aspects of pain perception such as pain catastrophization, if present the patient suffers a more intense pain experience and emotional distress [192]. The level of catastrophization has been shown to affect quality of life to a higher extent than pain intensity [193]. Patients with negative affect as well as those with a high level of catastrophization have shown a lower level of benefit of pain treatment [182], which is why they are often excluded in chronic pain trials.

There are several ways of measuring pain. NRS is the recommended tool to measure pain intensity in chronic pain treatment trials [194], supplemented with assessment of physical and emotional functioning, participant satisfaction, adverse events and adherence to treatment [195]. In **study III** we combined NRS with EHP, PCS with satisfaction assessment at the end

of trial, continuous reporting of adverse events and adherence to fulfill those recommendations.

There are several endpoints for reporting results in pain treatment trials such as mean values of NRS, maximum values of NRS, reduction of mean or maximum values of NRS where a 30 to 50 % reduction in considered clinically significant [196] and can identify potential responders and non-responders. Numbers needed to treat (NNT) is also used to report results, however, both NNT analysis and responder/non-responder endpoints require larger sample sizes for adequate power [197].

Research for new pharmacological treatment is usually initiated with a trial made for "proof of concept", which Schwertner [150] had conducted. Dose-finding studies are what follows. We conducted **study III** with a higher dose but with a smaller effect which was surprising as preclinical studies have suggested dose-dependent relationship both in terms of analgesic and anti-oxidative effect.

Perhaps we can only show a regression to the mean in our studies but given preclinical studies on melatonin and pain and the one human study with good clinical effect on endometriosis-associated pain there is reason to do more studies within the area of melatonin and endometriosis and dysmenorrhea. The treatment options for dysmenorrhea and endometriosis are scarce, especially for those wishing to conceive, and for many tainted with adverse effects.

7 CONCLUSIONS

Study I

There is a high prevalence of dysmenorrhea among teenagers in Stockholm with a high level of social and academic impairment but with a low tendency to seek medical attention and a sub-optimal therapeutic management.

Study II

Ten milligrams of melatonin given at bedtime during the menstrual week showed no clinically significant difference in the level of dysmenorrhea compared with placebo and no difference in the use of analgesics. Tolerability was high.

Study III

Twenty milligrams of melatonin given at bedtime during two menstrual cycles/months showed no clinically significant difference in the level of endometriosis-associated pain compared with placebo, no reduction of the use of analgesics or improvement of quality of life. Tolerability was high.

8 ETHICAL CONSIDERATIONS

All studies in this thesis were reviewed and approved by Regional Board of Ethics in Stockholm, Sweden (Dnr 2016/2332-31/4 and 2017/1177-21/2).

In study I anonymity was maintained as SIFO-KANTAR had the data base of the study population and we received the anonymized results.

In study II & III all data is presented in level of population, not individual level, securing anonymity. Some questions in the surveys could be perceived as private, there was always the option of "I don't know/not relevant" or skipping the question.

In clinical trials the risk-benefit estimate is of great importance, the trials were conducted in concordance with the declaration of Helsinki [198]. Melatonin has shown to have a benign safety profile, limiting the potential risks of the trials. We made sure a consent was given, the data was handled anonymously, and the participants could withdraw from study participation at any time without stating any reason. The participants could continue with their usual analgetic regimen, which otherwise can be an ethical challenge in pain trails.

9 FUTURE PERSPECTIVES

Severe dysmenorrhea in young girls is common and we cannot predict who will get CPP and/or endometriosis. Perhaps a screening system including all young women could be administered through the school health care to identify affected individuals who then would be referred to a general practitioner or a gynecologist for treatment.

Treating severe dysmenorrhea in young women to a higher extent, may help to alleviate suffering and may even reduce incidence of chronic pelvic pain due to severe dysmenorrhea. The progressive trait of endometriosis could perhaps be attenuated if young girls with dysmenorrhea were amenorrheic, which could hypothetically affect their fertility later in life. It may also raise awareness which could attenuate normalization of disabling dysmenorrhea and instead motivate young women to use and optimize available treatment to reduce the negative effect of dysmenorrhea.

Pre-clinical trials suggest that melatonin possesses anti-estrogen, anti-oxidative, analgesic and anxiolytic properties which, in theory, are what is needed to affect endometriotic cells, to impair growth and to alleviate pain. Further studies are needed to shed light on the mechanisms behind those properties.

Studies on mice have shown melatonin to reduce the size of endometriotic lesions, perhaps trials on primates would be of a higher clinical relevance due to them having more similarities with humans than mice who do not have a uterus.

Considering the low bio-availability (approximately 15%) and the suspected high inter-personal variability [199], serum melatonin would be interesting to measure in future trials with melatonin. Stipulating that oral administration results in melatonin concentrations too low to achieve any anti-oxidative effect on endometriotic lesions in humans, a local application may be of use. Vaginal administration has shown a longer half-life and a higher bioavailability [200] perhaps a vaginal ring with melatonin could be effective.

However, the high cost for both the administrative process and for placebo drugs, constitute a serious impediment to enable future academic trials.

10 POPULÄRVETENSKAPLIG SAMMANFATTNING

Mensvärk är vanligt förekommande i hela världen. Svår mensvärk kan vara ett tecken på endometrios, när celler som liknar dem som är inne i livmodern växer utanför livmodern. Där kan cellerna orsaka inflammation, smärta och ibland infertilitet. Tillgänglig behandling består av smärtstillande och hormonell behandling som till exempel p-piller. Vid endometrios kan man också behandla hormonellt för att åstadkomma ett reversibelt kemiskt klimakterium, eller med operation. Dessa behandlingar är inte lämpliga för alla och kan ge biverkningar.

I **studie I** skickades ett frågeformulär till alla flickor födda år 2000 och folkbokförda i Stockholm (3998 till antalet), som då var 16-17 år. Totalt 45% svarade (1780) och av dessa angav 89% mensvärk varav 36% svår mensvärk. Månatlig frånvaro från skolan rapporterades av 14% medan bara 7% hade besökt läkare för besvären.

Studie II- Fyrtio kvinnor med svår mensvärk, utan känd endometrios, lottades till att få 10 mg melatonin eller sockerpiller som såg identiska ut. Varken personalen eller deltagarna visste vilken behandling som lottades fram. Tabletterna togs varje kväll under mensveckan, 7 dagar i rad. Smärtan rapporterades varje kväll och efter 2 månaders behandling visade resultaten att melatonin inte var bättre på att smärtlindra än sockerpiller.

Studie III- Fyrtio kvinnor med endometrios-orsakad smärta lottades till att få 20 mg melatonin eller sockerpiller varje kväll. Efter två månaders behandling visade resultaten att melatonin inte var bättre på att smärtlindra än sockerpiller.

Det fanns ingen skillnad mellan grupperna i hur mycket andra smärtstillande tabletter studiedeltagarna tagit.

Tidigare studier har visat att melatonin har smärtstillande och anti-inflammatoriska egenskaper som teoretiskt vore bra för behandling av både mensvärk och endometrios. Ytterligare studier skulle vara av nytta för att se om melatonin ändå kan ha en plats i behandlingen av svår mensvärk och/eller endometrios.

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Sally and **Olga** – Our extraordinarily wonderful children. Life would be nothing without you.

12 QUESTIONNAIRE FOR STUDY I

Q001
Hur gammal är du?

Q002
Har du fått mens?
1 Ja
2 Nej
3 Vill ej uppge

Q003
Hur gammal var du när du fick mens första gången?

Q004
Har du haft mensvärk?
1 Ja
2 Nej
3 Tveksam/vet ej

Q005
Hur många dagar brukar du ha mensvärk och hur ont brukar du ha? Svara på en skala från 0 till 10 där 0 innebär ingen smärta och 10 värsta tänkbara smärta.

	0 Ingen smärta	1	2	3	4
	5	6	7	8	9	10
Värsta tänkbara smärta						
Dagen före mens	□	□	□	□	□	
	□	□	□	□	□	□
Dag 1	□	□	□	□	□	□
	□	□	□	□	□	
Dag 2	□	□	□	□	□	□
	□	□	□	□	□	
Dag 3	□	□	□	□	□	□
	□	□	□	□	□	
Dag 4	□	□	□	□	□	□
	□	□	□	□	□	
Dag 5	□	□	□	□	□	□
	□	□	□	□	□	
Dag 6	□	□	□	□	□	□
	□	□	□	□	□	

Q006
Tar du smärtstillande tabletter vid mensvärk när den är som värst?
1 Ja, varje månad
2 Ja, någon gång om året
3 Nej, aldrig
4 Tveksam, vet ej

Ask only if Q006 - Q006,1,2
Q007
Vilka av följande läkemedel tar du när mensvärken är som värst?
1 Alvedon, Panodil, pamol, pimex

2 Ipren, Ibumetin, Ibuprofen, Ifenin, Brufen
3 Naproxen/Pronaxen
4 Voltaren/Diklofenak
5 Tveksam, vet ej

Ask only if Q007 - Q007,1
Q008
Du svarade att du tar någon av tabletterna Alvedon, Panodil, pamol, pimex. Vilken styrka tar du när mensvärken är som värst?
1 Vanlig receptfri dos (500 mg)
2 1 g, receptbelagt
3 Vet ej

Ask only if Q007 - Q007,1
Q009
Hur många tabletter tar du i taget?

Ask only if Q007 - Q007,1
Q010
Upprepar du dosen under dagen?
1 Ja
2 Nej
3 Tveksam, vet ej

Ask only if Q007 - Q007,1 and Q010 - Q010,1
Q011
Hur många tabletter tar du om dagen?

Ask only if Q007 - Q007,2
Q012
Du svarade att du tar någon av tabletterna Ipren, Ibumetin, Ibuprofen, Ifenin eller Brufen. Vilken styrka tar du när mensvärken är som värst?
1 200 mg
2 400 mg
3 600 g, receptbelagt
4 Vet ej

Ask only if Q007 - Q007,2
Q013
Hur många tabletter tar du i taget?

Ask only if Q007 - Q007,2
Q014
Upprepar du dosen under dagen?
1 Ja
2 Nej
3 Tveksam, vet ej

Ask only if Q007 - Q007,2 and Q014 - Q014,1
Q015
Hur många tabletter tar du om dagen?

Ask only if Q007 - Q007,3
Q016
Du svarade Naproxen/Pronaxen. Vilken styrka tar du när mensvärken är som värst?
1 250 mg - receptfri dos
2 500 mg - receptbelagd dos
3 Vet ej

Ask only if Q007 - Q007,3
Q017
Hur många tabletter tar du i taget?

Ask only if Q007 - Q007,3
Q018
Upprepar du dosen under dagen?
1 Ja
2 Nej
3 Tveksam, vet ej

Ask only if Q007 - Q007,3 and Q018 - Q018,1
Q019
Hur många tabletter tar du om dagen?

Ask only if Q007 - Q007,4
Q020
Du svarade Voltaren/Diklofenak. Vilken styrka tar du när mensvärken är som värst?
1 25 mg - receptfri dos
2 50 mg - receptbelagd
3 Vet ej

Ask only if Q007 - Q007,4
Q021
Hur många tabletter tar du i taget?

Ask only if Q007 - Q007,4
Q022
Upprepar du dosen under dagen?
1 Ja
2 Nej
3 Tveksam, vet ej

Ask only if Q007 - Q007,4 and Q022 - Q022,1
Q023
Hur många tabletter tar du om dagen?

Ask only if Q006 - Q006,1,2
Q025
Sammanfattningsvis, hjälper värktabletterna du tar mot mensvärken?
1 Ja
2 Nej
3 Tveksam, vet ej

Ask only if Q006 - Q006,1,2
Q026
Tar du några av dessa preparat samtidigt/i kombination med varandra?
Kryssa för de du kombinerar
1 Alvedon, Panodil, pamol, pimex
2 Ipren, Ibumetin, Ibuprofen, Ifenin, Brufen
3 Naproxen/Pronaxen
4 Volatren /Diklofenak

Ask only if Q006 - Q006,3,4
Q024

Tar du något annat preparat mot mensvärk?
1 Ja, nämligen *Open
2 Nej

Q027
Har du gått till något av följande ställen på grund av din mensvärk?
1 Skolsköterska
2 Ungdomsmottagning
3 Husläkare/vårdcentral
4 Gynekolog
5 Inget av dessa

Q028
Använder du något av följande?
1 P-piller (Prionelle,Neovletta, Abelonelle, Yasmin, Yasminelle, Cerazette, Azalia, Vinelle)
2 P-stav
3 p-plåster
4 p-ring
5 Hormonspiral
6 Kopparspiral

Ask only if Q028 - Q028,1
Q029
Vilket p-piller använder du?
1 Prionelle
2 Neovletta
3 Abelonelle
4 Yasmin
5 Yasminelle
6 Cerazette
7 Azalia
8 Vinelle
9 Kommer inte ihåg vad den heter
10 Annat: *Open

Ask only if Q028 - Q028,1
Q030
Vad var anledningen till att du började med p-piller?

1 För att inte bli gravid
2 Mot mensvärk
3 Både för att inte bli gravid och mot mensvärk
4 Annat skäl *Open
5 Tveksam, vet ej

Ask only if Q030 - Q030,2,3
Q031
Hur länge har du tagit p-piller mot mensvärk?
1 Mer än 6 mån
2 Mindre än 6 månader
Ask only if Q030 - Q030,2,3
Q032
Har det hjälpt mot mensvärken?
1 Ja
2 Nej

Ask only if Q028 - Q028,2
Q033
Vad var anledningen till att du började med p-stav?
1 För att inte bli gravid
2 Mot mensvärk
3 Både för att inte bli gravid och mot mensvärk
4 Annat skäl *Open
5 Tveksam, vet ej
Ask only if Q033 - Q033,2,3
Q034
Hur länge har du använt p-stav mot mensvärk?
1 Mer än 6 mån
2 Mindre än 6 månader

Ask only if Q033 - Q033,2,3
Q035
Har det hjälpt?
1 Ja
2 Nej
3 Tveksam, vet ej

Ask only if Q028 - Q028,3
Q036
Vad var anledningen till att du började med p-plåster?
1 För att inte bli gravid
2 Mot mensvärk
3 Både för att inte blir gravid och mot mensvärk
4 Annat skäl *Open
5 Tveksam, vet ej

Ask only if Q036 - Q036,2,3
Q037
Hur länge har du använt p-plåster mot mensvärk?
1 Mer än 6 mån
2 Mindre än 6 månader

Ask only if Q036 - Q036,2,3
Q038
Har det hjälpt?
1 Ja
2 Nej
3 Tveksam, vet ej

Ask only if Q028 - Q028,4
Q039
Vad var anledningen till att du började med p-ring?
1 För att inte bli gravid
2 Mot mensvärk
3 Både för att inte bli gravid och mot mensvärk
4 Annat skäl *Open
5 Tveksam, vet ej

Ask only if Q039 - Q039,2,3
Q040
Hur länge har du använt p-ring mot mensvärk?
1 Mer än 6 mån
2 Mindre än 6 månader

Ask only if Q039 - Q039,2,3
Q041
Har det hjälpt?
1 Ja
2 Nej
3 Tveksam, vet ej

Ask only if Q028 - Q028,5
Q042
Vad var anledningen till att du började med hormonspiral?
1 För att inte bli gravid
2 Mot mensvärk
3 Både för att inte bli gravid och mot mensvärk
4 Annat skäl *Open
5 Tveksam, vet ej

Ask only if Q042 - Q042,2,3
Q043
Hur länge har du haft hormonsprial mot mensvärk?
1 Mer än 6 mån
2 Mindre än 6 månader

Ask only if Q042 - Q042,2,3
Q044
Har det hjälpt?
1 Ja
2 Nej
3 Tveksam, vet ej

Ask only if Q028 - Q028,6
Q045
Vad var anledningen till att du började med kopparspiral?
1 För att inte bli gravid
2 Mot mensvärk
3 Både för att inte bli gravid och mot mensvärk
4 Annat skäl *Open
5 Tveksam, vet ej

Ask only if Q045 - Q045,2,3
Q046
Hur länge har du haft kopparspiral mot mensvärk?
1 Mer än 6 mån
2 Mindre än 6 månader

Ask only if Q045 - Q045,2,3
Q047
Har det hjälpt?
1 Ja
2 Nej
3 Tveksam, vet ej

Q048

	Aldrig	Någon gång om året	Varje månad
svimmat pga mensvärk?	□	□	□
kräkts pga mensvärk?	□	□	□
ont när du kissar?	□	□	□
ont när du bajsar?	□	□	□
upplevt extreme trötthet?	□	□	□
mensvärk som inte går över med smärtstillade tabl?	□	□	□
stannat hemma från skolan pga mensvärk?	□	□	□
skrivit sämre på ett prov pga mensvärk?	□	□	□
huvudvärk?	□	□	□
migrän?	□	□	□

Q049 - Q049

Den dagen mensen är som rikligast:

	Aldrig	Någon gång om året	Varje månad
Blöder du klumpar?	□	□	□
Behöver du använda både tampong och binda samtidigt?	□	□	□
Blöder du igenom dina kläder?	□	□	□

Q050
Har du haft sex någon gång?
1 Ja
2 Nej

Q051
Om ja, har du haft ont vid eller efter samlag?

1 Ofta
2 Ibland
3 Aldrig

Q052
Har du ont i magen även när du inte har mens?
1 Ja
2 Nej

Ask only if Q052 - Q052,1
Q053
Om ja, har du fått en diagnos som förklarar ditt magont?
1 Ja
2 Nej

Ask only if Q053 - Q053,1
Q054
Om ja, vilken diagnos?

Q055
Gör mensvärk ibland att du inte är med på sånt som du tycker är kul; t.ex. träffa kompisar, gå och träna, åka på resa?
1 Ja
2 Nej
3 Tveksam, vet ej

Q056
Röker du?
1 Ja
2 Nej
3 Tveksam, vet ej

Q057
Finns det någon i din familj som har besvär med mensvärk?

1 Ja, mamma
2 Ja, syster/systrar
3 Både mamma och syster/systrar
4 Annan, vem? *Open
5
6 Nej
Tveksam, vet ej

Q058 -
Känner du dig ledsen när du tänker på din mensvärk?
1 Ja
2 Nej

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