Prevalence, impact and management of dysmenorrhea among the female students at the University of Split School of Medicine

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PREVALENCE, IMPACT AND MANAGEMENT OF DYSMENORRHEA AMONG THE FEMALE STUDENTS AT THE UNIVERSITY OF SPLIT SCHOOL OF MEDICINE

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1. INTRODUCTION

1.1. Dysmenorrhea Definition and Prevalence

Primary dysmenorrhea is referred to as cramping pain in the lower abdomen occurring just before or during menstruation, in the absence of other pelvic diseases such as endometriosis or uterine fibroids. Primary dysmenorrhea only occurs in ovulatory cycles (1,2).

Dysmenorrhea occurring in anovulatory cycles is considered to be secondary dysmenorrhea (3). Pain from primary dysmenorrhea can therefore be relieved by administration of oral contraceptive pills, which inhibit ovulation.

Primary dysmenorrhea is the most common gynecological complaint among young women. For women of reproductive age worldwide, dysmenorrhea is more prevalent than the other 2 common types of chronic pelvic pain, dyspareunia and non-cyclical chronic pelvic pain (3).

The reported prevalence rate for dysmenorrhea in women of reproductive age ranges from 43 to 90%. This wide range in the reported prevalence rate is primarily due to absence of standardized tests for diagnosis and measurement of dysmenorrhea (4).
In general, a greater prevalence has been observed in young women, with an estimated occurrence ranging from 67% to 90% for those aged 17–24 years (1,2).

Despite the high occurrence with associated negative effects, a large proportion of adolescence do not seek medical care. Appropriate counselling and therapy should be offered to all females to help them cope with the many challenges of dysmenorrhea. Usually appearing within 6–12 months after the menarche, primary dysmenorrhea occurs almost invariably in ovulatory cycles (5,6).

1.2. Clinical Presentation

In addition to painful cramps, many women with dysmenorrhea experience other menstrual related symptoms including back and thigh pain, headaches, diarrhea, nausea and vomiting.

The clinical features of dysmenorrhea include frequent and crampy pain which mainly affects the lower abdomen and radiates to the back or thigh. Severe pain that limits daily activities is seen much less frequently and affects approximately 7%–15% of women (1).

At the same time, 41% of adolescents and young adults aged 26 years or less, reported that they had limitations in their daily activities due to dysmenorrhea (7). Another cross-sectional study among secondary school girls in Nigeria, showed that 13% of the women had at least one occasion of missed school or loss of activity due to painful cramps during their

menstrual cycle (8). These figures highlight the magnitude of dysmenorrhea as a problem as well as the complexity of measuring its prevalence.

1.3. Risk Factors

A range of risk factors for dysmenorrhea have been identified throughout the literature. In general, the severity of dysmenorrhea has been suggested to relate to age (9), smoking (10,11) higher body mass index, earlier age at menarche (12), nulliparity, longer and heavier menstrual flow (13), and family history of dysmenorrhea (14). Women using oral contraceptives generally report less severe dysmenorrhea (13,15).

In the study at the East Hospital in Gothenburg the factors influencing the prevalence and severity of dysmenorrhea were assessed longitudinally in a representative sample of young women born in 1962 (13). Factors of possible importance for the prevalence and severity of dysmenorrhea were analyzed separately, taking into account relevant background factors. The prevalence and severity of dysmenorrhea stayed unchanged in women who were still nulliparous in 1986, while women who gave birth eliminated menstrual pain. However, no difference regarding the prevalence and severity of dysmenorrhea after an abortion or miscarriage was observed. A possible explanation for this difference is the influence of pregnancy on uterine neuro-transmitters, which can be seen on histology samples, and the reduction or disappearance of dysmenorrhea after childbirth (6). During the last trimester of human pregnancy, a close to complete reduction of uterine adrenergic nerves and decreased uterine noradrenaline has been demonstrated (13).

1.4. Pathophysiology

There are multiple theories regarding the contributing factors of dysmenorrhea, of which many still need to be tested. Initiation of menstruation is marked by a decrease in both circulating progesterone and estradiol, causing an increased transcription of endometrial collagenases, matrix metalloproteinases (MMPs), and inflammatory cytokines. Upregulated MMPs target and break down endometrial tissue, leading to release of phospholipids from the cellular membrane. Uterine phospholipases convert phospholipids to arachidonic acid, which can then be synthesized into prostaglandins (PG), prostacyclins, and thromboxane-2a via cyclooxygenase (COX)-1 and -2. The expression of COX-2 is highest during menses.

Even though it is unclear whether increased COX-2 expression occurs in dysmenorrhea, the end products PGE_2 and $PGF_{2\alpha}$ are elevated in the menstrual fluids of dysmenorrheic women when compared to healthy controls (16).

1.4.1. Prostaglandins

The 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 (17). 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 (17).

Today it is believed that women with primary dysmenorrhea have an increased uterine activity, secondary to elevated levels of prostaglandins. These prostaglandins are produced and released by the endometrial tissue at the time of menstruation. The cause of this increased prostaglandin production and release is at present unknown. Because of the hypercontractility of the uterus at menstruation in women with primary dysmenorrhea, blood flow to the uterus is compromised and uterine ischemia occurs (18).

Most of the clinical symptoms can be explained by the action of uterine prostaglandins, especially by PGF 2a. PGF2a is a natural prostaglandin used in medicine to induce labor, as an abortifacient, in the treatment of hydatidiform moles and for postpartum hemorrhage. It is produced by the uterus and stimulated by oxytocin in the event of implantation in the luteal phase (19). It also highlights pain sensitivity in women with dysmenorrhea and makes the case for it being classified as a central sensitization syndrome, a condition of the nervous system that is associated with the development and maintenance of chronic pain (20).

During the monthly shedding of the endometrium, the disintegrating endometrial cells release PGF2a as the menstruation begins. The PGF2a stimulates myometrial cells to contract in order to cause endometrial sloughing. The contraction also leads to ischemia and sensitization of nerve endings. The clinical evidence for this explanation of dysmenorrhea is supported by the fact that women with more severe menstrual pains have higher levels of circulating PGF2a in their menstrual fluids. The levels of PGF2a are highest during the first two days of menstruation which correlates with the peak of symptoms. In addition to this, multiple studies have shown the efficacy of NSAIDs as pain relief, which acts via prostaglandin synthetase inhibition (21–23).

To synthesize PGs, free fatty acid precursors for arachidonic acid are needed, and therefore these are the limiting factor when PGs are produced in the body. The availability of free fatty acid precursors is regulated by cyclic adenosine phosphate. Via cyclic adenosine phosphate, PG production can be stimulated by substances such as adrenalin, peptide hormones and steroid hormones, but also by mechanical stimuli and tissue trauma (10).

Arachidonic acid is derived from phospholipids by the lysosomal enzyme phospholipase A2 (24,25). The stability of lysosomal activity, mainly phospholipase A2, is regulated by several factors, one of which is progesterone levels is important. High progesterone levels tend to stabilize the activity of lysosomes, while falling or low levels tend to destabilize lysosome activity. This decrease in progesterone causes the stabilizing effect on endometrial lysosomes to be removed. This in turn causes a release of phospholipase A2, menstrual flow and hydrolysis of phospholipids from cell membranes in order to generate more arachidonic acid (26).

As more arachidonic acid is produced at the same time as there is intracellular destruction and tissue trauma from menstrual shedding, an increased production of prostaglandins is favored (22,23). Consequently, all women have increased levels of prostaglandins during the luteal phase compared with the follicular phase of ovulatory cycles.

Levels of prostaglandin F- 2alpha (PGF-2a) and prostaglandin E (1) are low in the proliferative phase of the cycle (10-25 ng/100 mg tissue). PGF-2a then rises significantly during the luteal phase to levels of 65-75 ng/100 mg of tissue (26).

Even if prostaglandins could stimulate nociceptors and cause pain, it has been suggested that prostaglandins cause cramping pain indirectly, via stimulation of uterine contractions (16).

Recognition of elevated PGE_2 and $PGF_{2\alpha}$ in patients suffering from dysmenorrhea, has high-lighted the idea of inhibiting COX-2 with NSAIDs to treat menstrual pain. Non-specific NSAIDs are those that bind to both COX-1 and COX-2 to inhibit prostaglandin synthesis. Selective NSAIDs known as COX-2 inhibitors reduce menstrual pain by specifically inhibiting COX-2 activity. In difference to COX-1, which is always expressed (27), COX-2 is upregulated by inflammation associated stimuli and during withdrawal of progesterone (28,29). These properties of COX-2 inhibitors make it an appropriate alternative to non-specific NSAIDs.

$PGF_{2\alpha}$ administration has been proved to stimulate uterine contractility and elicit visceral pain (16), and drugs that blocks prostaglandin synthesis, such as ibuprofen and naproxen, have been shown to reduce uterine contractility in dysmenorrheic women (16). These findings suggest that prostaglandins cause uterine contractility and cramping pain via temporary elevations in uterine pressure (5). Since not all women with menstrual pains show alterations in uterine pressure (30) alternative mechanisms also contributes to menstrual pain.

One example is the impaired uterine perfusion that can be seen in patients with dysmenorrhea. has been observed in dysmenorrhea (31) leading to ischemia which may also cause cramping pain.

1.4.2. Endocrine factors of dysmenorrhea

The only proven endocrine factor is the occurrence of primary dysmenorrhea in ovulatory cycles. In anovulatory cycles and in women on the oral contraceptive pill, primary dysmenorrhea does not occur. Thus, in dysmenorrhea associated with anovulatory cycles, careful examination for a pelvic pathology must be performed (32).

The hormones produced in the neurohypophysis, vasopressin and oxytocin may play a role in the etiology of primary dysmenorrhea. Women with the condition have shown increased plasma levels of both these hormones during early menstruation (33). In addition, administration of vasopressin stimulates uterine activity and reduces the blood flow to the uterus, which in turn leads to pain with the same character as that of primary dysmenorrhea (34). Both vasopressin and oxytocin have receptors expressed on the myometrium and uterine vessels. The vasopressin V1a receptor found in the uterus differs from the vasopressin V2 receptor in the kidneys, and the V1b receptor that is mainly found in the anterior part of the pituitary gland.

The involvement of vasopressin and oxytocin in the etiology of primary dysmenorrhea can further be explained by the therapeutic effect of inhibitors of both oxytocin and V1a receptor such as Atosiban and Relcovaptan (SR 49059) (35).

Gonadotropic hormones such as estradiol, follicle stimulating hormone (FSH) and luteinizing hormone (LH) influence the release of oxytocin and vasopressin from the hypophysis. Estradiol stimulates spontaneous and osmotically induced release of oxytocin and vasopressin, an effect which is counteracted by progesterone. The premenstrual plasma concentration of 17b-estradiol (17b-E2) has previously been shown to be significantly higher in healthy women compared with those suffering from dysmenorrhea (35).

Increased oxytocin levels may stimulate an increased FSH release that in turn may cause the release of preovulatory 17b-E2 in dysmenorrheic patients. Higher levels of 17b-E2 may explain the higher level of oxytocin seen in the plasma around the time of menstruation, which in turn could contribute to increased myometrial contractility (36).

1.5. Psychological risk factors

Even though there have not been any extensive studies of psychosocial risk factors of primary dysmenorrhea, there is increased evidence of psychological factors as an etiology of dysmenorrhea. Certain psychological factors such as high emotional disturbance, has been found to be associated with higher occurrence of dysmenorrhea. Previously performed studies reported that women with dysmenorrhea have an increased tendency to be more preoccupied

with bodily sensations, express more negative attitudes against illness and more negative attitude regarding menstruation than do other women. Lack of social support was the most common single cause of psychological stress related to dysmenorrhea (37).

1.6. Pain

The current definition of pain by the International Association for the Study of Pain defines it as “an unpleasant sensory and emotional experience associated with an actual or potential tissue damage”, or described in terms of such disease (38).

Pain can be classified according to different categories. The most common ways to differentiate different types of pain are acute vs chronic, and the underlying mechanism such as nociceptive vs psychogenic. Acute pain is short-term pain with a sudden onset and a specific cause, commonly tissue injury. It generally lasts for fewer than six months and goes away once the underlying cause is treated. Chronic pain lasts for more than six months, even after the original injury has healed (39).

The most common type of pain is so-called nociceptive pain. It is caused by stimulation of nociceptors, which are pain receptors for tissue injury. The mode of stimulation can be further classified into “thermal” e.g. heat or cold stimulated, “mechanical” such as crushing or tearing and “chemical” which is seen during inflammation or when for example iodine is put into an open wound. Some nociceptors respond to more than one type of stimuli and are then called polymodal (40). Different nociceptors also have different sites of origin. Examples of locations are “visceral”, “deep somatic”, “superficial somatic” pain.

Visceral structures such as the heart, liver and intestines are highly sensitive to stretch, ischemia and inflammation, but relatively insensitive to other stimuli that commonly causes pain e.g. burning and cutting. Visceral pain is diffuse and difficult to locate and may be accompanied by nausea and vomiting. It has been described as dull, deep and sickening.

Somatic pain results when pain receptors in the tissue, instead of in the internal organs, are stimulated. Examples of such tissue could be skin, muscles, joints and bones. It’s often easier to pinpoint the location of somatic pain rather than visceral pain. Somatic pain is further divided in ‘deep’ vs ‘superficial’, where deep somatic pain refers to aching pain that is felt in your joints, tendons, bones, and muscle. Superficial somatic pain is felt in your skin and mucous membranes and is usually sharp or throbbing in character (41).

Neuropathic pain is the result of a default in this system, when damaged or dysfunctional nerves are misfiring pain signals. This type of pain differs from the more common somatic pain, as it does not require a pain stimulus and seems to come out of nowhere,

rather than as a response to any specific injury. In the same way, neuropathic pain can also be pain felt in response to things that aren't usually painful such as cold air or clothing against your skin (42).

The pain threshold is the point along the curve of increasing perception of a stimulus where pain is initially felt. It is a very subjective phenomenon and hard to measure accurately. It is important to distinguish between the external stimulus which can be measured easily with for example a thermometer and the person's or animal's resulting pain perception, which is an internal experience. Sometimes these internal perceptions may be measured indirectly via psychometric responses and questionnaires such as a visual analogue scale (VAS) (38).

The Visual Analogue Scale (VAS) is the most often used scale for quantification of endometriosis related pain and for dysmenorrhea. Together with a numbered rating scale and another scale assessing the global clinical impression and quality of life, this is the considered the best pain scale to grade the severity of dysmenorrhea (43,44).

1.6.1. Pain perception during the menstrual cycle

Endogenous opioids produced in the body seem to play a significant role in pain perception. In a study the pain threshold was seen to elevate in times of increased sex hormones, such as during pregnancy (45). In another study, via simulated pregnancies in rats, a statistically significant elevation of the pain threshold mediated via an endogenous opioid system was demonstrated (49).

The menstrual cycle has been reported to alter pain perception in females but the patterns differ among studies (50). There is no strict role about how to divide the phases of the menstrual cycle. In Ferin, Jewelewicz, and Warren divide the menstrual cycle into three phases: (1) the follicular phase (from the first day of menstruation to ovulation at the time for follicular growth), (2) the ovulatory period (when the secretion of gonadotropin-releasing hormone from the hypothalamus which in turn increases the pituitary glands' production of both the luteinizing hormone and the follicle-stimulating hormone and the rise in estrogen to its peak), and (3) the luteal phase (the time from ovulation to the beginning of menstruation) during this time levels of both progesterone and estrogen rise and reach a maximum about 6-9 days after the gonadotropin surge (51).

Hapidou and Rollman found that the tender points by palpation were more painful in the follicular phase than in the luteal phase in women with normal cycles (52). Riley and colleagues performed a meta-analysis of 16 published studies of associations between the perception of experimentally induced pain across the menstrual cycle phases of healthy

women. Analysis showed that higher pain threshold was consistently found during the follicular phase (Days 6-11) of the menstrual cycle than during later phases (46).

1.7. Pain management

There are several medications used for the treatment of primary dysmenorrhea, such as non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, physical therapy and Chinese traditional therapies. Among them the non-steroidal anti-inflammatory drugs are the first-line treatment. As aforementioned, recent studies suggest that increased endometrial prostaglandin production and release may be responsible for dysmenorrhea. Prostaglandins cause myometrial contractility that, if excessive, leads to uterine ischemia and pain (53).

First, there is a striking similarity between the clinical manifestations of primary dysmenorrhea and the symptoms induced when exogenous prostaglandins E_2 or $F_{2\alpha}$ are administered. In both situations, uterine contractions occur, and diarrhea, vomiting, and nausea are common. In the secretory phase of menstrual cycle, the endometrium which is under the influence of progesterone, has higher concentrations of prostaglandins than does proliferative endometrium. Endometrium in anovulatory cycles does not have an increase in prostaglandin secretion (54). Many nonsteroidal anti-inflammatory drugs that are prostaglandin synthetase inhibitors have to be effective in the treatment of primary dysmenorrhea.

A Cochrane review of 73 randomized controlled trials (RCTs) demonstrated strong evidence to support nonsteroidal anti-inflammatory drugs (NSAIDs) as the first-line treatment for primary dysmenorrhea (55).

Today a wide range of NSAIDs are used as analgesics and anti-inflammatory agents through inhibiting cyclooxygenase (COX) enzymes including COX-1 and COX-2. The pain relieve ability of NSAIDs is mainly attributed to COX-2 enzymes inhibition—an important pathway related to hormone release and the process of inflammation, while their adverse effects (such as indigestion, headaches, and lethargy, which are considered to be the most concerning adverse effects in PD patients) are thought to be involved with the COX-1 enzymes inhibition.

The choice of NSAID should be based on effectiveness and tolerability for the individual patient, because no NSAID has been proven more effective than others. Randomized control trials have shown that all different types of NSAIDs except aspirin were significantly more efficacious than placebo. However, there is no significant difference between each pair of NSAIDs (53).

Non-steroidal anti-inflammatories (NSAIDs) are the preferred first line analgesics in the treatment of dysmenorrhea. Regular use has shown a 27-35% improvement in dysmenorrhea (56). Many studies have consistently reported that ~58% to 70% of Western adolescent girls self-medicate with non-steroidal anti-inflammatory drugs and analgesic medicine for dysmenorrhea (57).

NSAIDs, such as ibuprofen and naproxen sodium, are often used as first-line therapy. These drugs, and COX-2 selective NSAIDs such as celecoxib, have both anti-inflammatory and analgesic effects through inhibition of the COX-2 enzyme. Both nonselective and COX-2 selective NSAIDs have been associated with an elevated risk of serious gastrointestinal side effects, such as ulcers and bleeding. Celecoxib however, shows a lower rate of gastric discomfort and dyspepsia when compared to non-selective NSAIDs drugs (6).

Multiple clinical trials have been able to show the efficacy of administering NSAIDs in order to relieve pain of primary dysmenorrhea. The same drugs are also efficient in reducing pain from IUD-induced dysmenorrhea, which also is the result of elevated levels of prostaglandins (4).

Some NSAIDs have shown to relieve pain and to be associated with a significant decrease in menstrual fluid prostaglandin levels (58). The choice of NSAID should be based on effectiveness and tolerability for the individual patient, because no NSAID has been proven more effective than others. Randomized control trials have shown that all different types of NSAIDs except aspirin were significantly more efficacious than placebo (53,58).

Ibuprofen is a propionic acid derivative that quickly gets absorbed by the gastrointestinal tract. The blood concentrations peak 1-2 hours after a single oral dose. More than 90 percent of ibuprofen is metabolized in the liver to inactive metabolites. The metabolites are then excreted in the urine within 24 hours of the last oral dose. The recommended dose for patients with dysmenorrhea is 400 to 800 mg as an initial dose, followed by 400 mg four times a day (59).

In one study 33 dysmenorrheic patients were given ibuprofen, aspirin and a placebo in a double-blind crossover study, with each drug taken during one of three successive menstrual cycles in random sequence. Paired drug comparisons demonstrated the statistical superiority of ibuprofen, as compared with the other two, for the relief of pain (58). Unless the patient wishes to use oral contraceptives for birth control, ibuprofen has often been prescribed as the drug of choice because it only needs to be given for two to three days each cycle, does not suppress the pituitary ovarian axis, and does not cause metabolic alterations. Clinical trials have shown ibuprofen to be highly efficacious, and more effective than indomethacin, aspirin,

or propoxyphene, with no or few side effects (60). It has been shown to be more readily tolerated than aspirin and at least three times as potent (61).

In a series of reviews the Department of Obstetrics and Gynecology at the University of Auckland, New Zealand, looked at 80 randomized controlled trials (RCTs) including a total of 5820 women and compared 20 different types of NSAIDs with placebo paracetamol or each other. The review found that NSAIDs appear to be very effective in relieving period pain and appear to work better than Paracetamol but commonly cause adverse effects including indigestion, headaches and drowsiness. When compared to placebo, the evidence suggests that if 10% of women taking placebo experience side effects, between 11% and 14% of women taking NSAIDs can expect the same problems (53).

Paracetamol, also known as acetaminophen, is a medication commonly used to treat fever and pain. Despite its common use, the mechanism of action is not yet completely understood. When compared to NSAIDs such as aspirin, paracetamol does not appear to inhibit the function of any of the cyclooxygenase (COX) enzymes outside the central nervous system. This appear to be the reason why it is not useful as an anti-inflammatory drug.

Instead it seems that paracetamol provides its analgesic effect via central anti-nociceptive actions that specifically inhibits COX-3, a variant of COX-1 pathway. In addition to this, evidence suggests that paracetamol activates serotonergic descending pathways that are able to inhibit nociceptive signal transmission within the spinal cord. The most significant advantage of paracetamol is that it does not cause gastrointestinal bleeding or dyspepsia (62). Paracetamol has been shown to help relieve menstrual pain and research shows that medicines combining 500 mg of paracetamol plus 65 mg of caffeine are more effective for menstrual pain than paracetamol alone (63).

Healthy adults without decreased liver function can take up to 4,000 mg per day without evidence of toxicity. Paracetamol is metabolized by the liver and when the recommended maximum dose is exceeded there is risk of hepatotoxicity. Therefore, side effects are multiplied when combined with alcohol and are more prone to occur in chronic alcoholics or people with decreased liver function (62).

Other possible side effects include skin reactions of different severity, with the most severe being possible fatal skin reactions such Steven-Johnson syndrome and toxic epidermal necrolysis. Prescription-strength products would be required to carry a warning label about skin reactions.

Buscopan, a quaternary ammonium compound and a semisynthetic derivative of hyoscine hydrobromide (scopolamine) is frequently used as pain relief in patients with

dysmenorrhea. It is effective in treating abdominal pain and is able to reduce the first stages of labor, without being associated with adverse outcomes in the mother or the neonate. The drug does not cross the blood-brain barrier, which minimizes undesirable central nervous system side effects that are usually associated with scopolamine/hyoscine (64).

Due to its spasmolytic nature, it is frequently used for spasmodic dysmenorrhea. It has been used to relieve spasm of the smooth muscle of the gastro-intestinal, biliary and urinary tracts, and also in the management of labor (65). It has also been used during abdominal or pelvic MRI or CT scans in order to improve the quality of pictures (66).

Treatment of dysmenorrhea is a well-accepted off-label use for oral contraceptive pills (OCPs). The OCPs can reduce the number of prostaglandins produced by glands in the lining of the uterus. This mechanism will reduce both uterine blood flow and cramps.

Consistent observational data support a beneficial effect from oral contraceptives in the treatment of dysmenorrhea. An RCT of women who took desogestrel-containing OCPs, showed that these women had less pain during menses than women who received placebo (67). Most women who receive depo-administered contraceptives are amenorrheic within the first year of use. Similarly, extended-cycle use of OCPs (i.e. taking OCPs for >12 weeks followed by one week off) leads to less-frequent menstrual periods. In a retrospective review, 21 % of women who chose extended-cycle regimens did so primarily for treatment of dysmenorrhea (68).

Although non-steroidal anti-inflammatory drugs are able to ease menstrual pain, some women with dysmenorrhea are unresponsive, and have to try less studied strategies.

A review of 51 different clinical trials found that 18% of women report minimal or no relief of menstrual pain with NSAIDs (69). This failure to relieve pain suggests multiple pathological mechanisms may contribute to treatment unresponsiveness. To find the explanation for these mechanisms is of critical need in gynecological research.

1.8. Anatomical factors contributing to dysmenorrhea

A subset of women with dysmenorrhea, particularly those with delayed presentation after menarche, may have separate anatomical factors that contribute to the resistance, such as endometriosis, leiomyoma, or adenomyosis. These are examples of ‘secondary dysmenorrhea’ that could underlie NSAID resistance. Undoubtedly, surgical interventions for these structural issues address dysmenorrhea. For example, in a meta-analysis, laparoscopic excision of endometriosis was shown to reduce menstrual pain (70).

The molecular contributions of anatomical factors to secondary dysmenorrhea are limited. Immunohistology studies investigating endometriosis demonstrated that lesions have increased COX-2 expression, which led to corresponding increased prostaglandins and aromatase activity (71).

Ectopic endometrium can occur in adenomyosis patients. They show increased levels of transient receptor potential vanilloid 1 (TRPV1), a pain signalling protein and oxytocin receptor (72).

In addition, gene expression of myometrial regulators myostatin and MMP14 found during biopsies in patients with leiomyoma, were positively correlated to severe dysmenorrhea (73).

The contribution of anatomical factors in pathogenesis of dysmenorrhea, particularly in patients with NSAID unresponsiveness, is unclear. A meta-analysis has estimated as many as 29% of dysmenorrheic women may have moderate to severe endometriosis (74).

However, since most women do not undergo laparoscopic examination, it is difficult to identify all women with NSAID-resistant dysmenorrhea who have endometriosis. A small clinical study found that among 31 women with NSAID-resistant dysmenorrhea, 35% had endometriosis (75).

In a larger study (n=654), 25% of the participants which reported NSAID-resistant dysmenorrhea had ultrasound or magnetic resonance imaging that suggested endometriosis (76). It is important to note that symptoms of dysmenorrhea are nonspecific for endometriosis, and NSAIDs can be effective in relieving some cases of menstrual pain in women with endometriosis.

In one observational study of leiomyomas, 70% of women with fibroids used NSAIDs and 51% reported a reduction in symptoms (77).

Since it is unknown whether anatomical factors contribute to NSAID unresponsiveness, further research is needed to determine whether treatment strategies targeting anatomical factors are sufficient for addressing the causes of NSAID-resistant dysmenorrhea.

2. OBJECTIVES

Dysmenorrhea commonly affects young women of reproductive age and can have significant impact on social, academic and personal life. In addition to painful cramps, many women with dysmenorrhea experience other menstrual related symptoms including back and thigh pain, headaches, diarrhea, nausea and vomiting. The women usually do not seek professional medical help, but rather tend to self-medicate with over the counter drugs.

The aim of our study is to investigate the prevalence, impact and management of dysmenorrhea among female students of medical studies in English, medical studies in Croatian, dental medicine and pharmacy students at University of Split School of Medicine.

We plan to investigate and compare the main characteristics of menstrual cycle, menstruation associated symptoms and management of menstrual pain among the female students of four study programs at University of Split School of Medicine.

In our study we expect to find a high prevalence of female students suffering from dysmenorrhea and its associated symptoms. We further hypothesize that non-prescription drugs are used in high numbers among the participants and menstrual pains to have an impact on school absenteeism and performance.

3. MATERIALS AND METHODS

A cross-sectional study was carried out amongst the female students of four study programs: Medical studies in Croatian, Medical studies in English, Dental medicine and Pharmacy, enrolled at University of Split School of Medicine in Split, Croatia. All female students enrolled into one of the four studies were eligible as participants in this study.
The questionnaires were administered to students of all academic years (1 - 6 for medical studies and dental medicine, and 1 - 5 for pharmacy), in online version created in Google Docs during the period of three months, from April until June of 2020. The participation was voluntary, anonymous and without compensation.

A total of 273 female students, out of 858 enrolled at University of Split School of Medicine participated in this study.

The background and the aim of the research were explained in the first part of the questionnaire. In the questionnaire, the students gave their general data: socio-demographic characteristics such as age, study program and the year of the study. The students also provided the data on the main characteristics of their menstrual cycle, menstruation associated symptoms and management of menstrual pain.

The results were analysed using the Microsoft Office Excel 2016 program and JASP 0.9.2.0. A descriptive analysis was conducted, with the results expressed in frequencies and percentages for dichotomous variables, and as mean with standard deviation (SD) for continuous variables, which were initially tested for normality using Kolmogorov-Smirnov test.

The percentages were calculated for every outcome. Nonparametric χ^2 test was used to assess differences between groups and correlations between variables. The answers were given in the 5-point Likert scale. The results were grouped in three categories: never or rarely; sometimes; and often or always.

Our study determined statistically significance to be less than $P<0.05$.

The study was approved by the University of Split School of Medicine Ethical committee, Approval number: 2181-198-03-04-20-0044. The research has been conducted in full accordance with the World Medical Association Declaration of Helsinki.

The questionnaire is added as the supplementary material of the thesis.

4. RESULTS

In this study, 270 (31%) out of 858 female students from four programs participated: 65 (38%) of Medical studies in English, 108 (28%) of Medical studies in Croatian, 67 (42%) of students of Dental medicine, 30 (21%) of Pharmacy students (Table 1). Among the USSM students, 72% are females.

Table 1. The number of female students (N) that participated in the research and total number of enrolled female students per year of medical studies in English, medical studies in Croatian, dental medicine and pharmacy, academic year 2019/2020.

N , total	**Medicine in English**		**Medicine in Croatian**		**Dental medicine**		**Pharmacy**	
1st year	10	42	8	64	15	24	/	24
2nd year	15	37	10	64	13	23	18	25
3rd year	13	37	6	69	16	28	/	26
4th year	13	22	7	56	2	31	/	27
5th year	9	20	34	63	10	24	12	45
6th year	5	16	43	65	11	29	/	/
TOTAL	**65**	**172**	**108**	**381**	**67**	**160**	**30**	**145**

The mean age of the participants was 22.8 (SD±2,1), with minimum of 18, and maximum being 30. First year students were 19 years old on average, second year students 20, third year students 21, fourth year students 22, fifth 23 and sixth 24 years old. Mean age of students in different studies can be seen in Table 2.

The overall mean age of menarche for the participants was 12.7 years (SD±1.6). For the individual programs the mean age of menarche is stated in Table 2.

The total number of 69 (25.6%) students declared the use of contraceptives with significant difference between study programs: 29 or 44.6% being in the English medical

program, 20 (18.5%) of the students in Croatian medical program, 16 (23.9%) in dental medicine and 4 (13.3%) of pharmacy students (χ^2 =17.68, P<0.001). The most commonly used contraceptive was combined (progesterone-estrogen) oral contraceptive pills. The students named Diana-35, Nuvaring, Yazz, Dayla and Lyndinette, and the most common type stated was Diana-35.

Twenty percent of the participating students declared having a history of pelvic pathologies. The number of students with regular menstrual cycles is 198 or 74% (Table 2).

Table 2. General characteristics of female students of four study programs at University of Split School of Medicine that participated in the study.

	Medicine in English	Medicine in Croatian	Dental medicine	Pharmacy	Total
Age (Mean±SD)	22,7±2,3	23,8±1,9	21,8±1,7	21,4±1,6	22,8±2,1
Age of the first menarche (Mean±SD)	13,1±1,6	12,5±1,3	12,7±2,0	12,1±1,7	12,7±1,6
Use of contraceptives N, (%)	29 (44.6)	20 (18.5)	16 (23.9)	4 (13.3)	69 (25.6)
History of pelvic pathologies N, (%)	8 (12.3)	26 (24.3)	16 (23.9)	3 (10)	53 (19.7)
Regular menstrual cycle N, (%)	45 (70.3)	80 (74.1)	48 (71.6)	25 (83.3)	198 (73.6)

N= number of students

In total 22% of students stated their menstrual cycle lasted <28 days, 65% 28-35 days and 10% >35 days (Table 3). The additional 3% declared their cycles to be really irregular, therefore not being able to choose a category. Duration for the individual programs cycles of students in each study program is found in Table 3.

When reporting the days of menstrual bleeding, most of the students (68%) reported they had 5-7 days, 28% of students stated that they had less than 5 days of bleeding, while only 4% reported more than 7 days. There is a statistical difference between reported days of bleeding of different studies, with most of the medical studies in Croatian, dental and pharmacy

students reporting 5-7 days, while medical studies in English students mostly reported <7 days (χ^2 =20.8, P<0.01) (Table 3).

Table 3**.** The characteristics of the menstrual cycle of female students of four study programs at University of Split School of Medicine that participated in the study.

	Medicine in English	Medicine in Croatian	Dental medicine	Pharmacy	Total
Duration of menstrual cycle in days N, (%)					
<28	14 (22,6)	22 (20,4)	10 (14,9)	13 (43,3)	59 (22,1)
28-35	36 (58,1)	74 (68,5)	48 (71,6)	15 (50,0)	173 (64,8)
>35	8 (12,9)	8 (7,4)	9 (13,4)	2 (6,7)	27 (10,1)
Days of menstrual bleeding N, (%)					
<5	30 (48,4)	27(25,2)	15 (22,4)	3 (10,0)	76 (28,2)
5-7	29 (46,8)	77 (72,0)	48 (71,6)	26 (86,7)	180 (67,7)
>7	3 (4,8)	3 (2,8)	4 (6,0)	1 (3,3)	11 (4,1)

N= number of students

When investigating menstrual associated symptoms, we asked the participants to grade the magnitude of their problems on a scale from 1-5, with 1 indicating never having problems, 2 rarely, 3 sometimes, 4 often, and 5 indicating always experiencing the problem. The answers 1 and 2 were then grouped into category never or rarely, and 4 and 5 into the category often or always.

Among the all participants about 98% of students reported to have some kind of menstruation associated symptoms (problem graded >2 on the scale). The most frequent symptom was pain and the least common was vomiting. About 58% of students stating to have experienced pain often or always, 11% nausea, 2% vomiting, 56% bloating, 16% reflux, 54% change in appetite, 29% headache, 12,2% dizziness and 45% lower back pain (Table 4).

Table 4. Menstruation associated symptoms reported by female students of four study programs at University of Split School of Medicine that participated in the study.

	Never or rarely, N (%) Often or always, N (%)				
	Medicine in English	Medicine in Croatian	Dental medicine	Pharmacy	**Total**
Pain	13 (20,0) 32 (49,2%)	21 (19,4) 66 (61,1%)	6 (9,0) 42 (62,7%)	7 (23,3) 16 (53,3)	**47 (17,4)** **156 (57,8)**
Nausea	47 (72,3) 6 (9,2)	78 (72,2) 10 (9,3)	45 (67,2) 9 (13,4)	18 (60,0) 4 (13,3)	**188 (69,6)** **29 (10,7)**
Vomiting	62 (95,4) 1 (1,5)	97 (90,7) 2 (1,9)	60 (89,6) 2 (3,0)	26 (86,7) 1 (3,3)	**245 (91,1)** **6 (2,2)**
Bloating	13 (20,0) 40 (61,5)	30 (28,0) 56 (52,3)	17 (25,4) 41 (61,2)	8 (26,7) 14 (46,7)	**68 (25,3)** **151 (56,1)**
Indigestion /reflux	42 (64,6) 10 (15,4)	60 (55,6) 24 (22,2)	41 (61,2) 9 (13,4)	23 (76,7) 1 (3,3)	**166 (61,5)** **44 (16,3)**
Change in appetite	17 (26,2) 33 (50,8)	18 (16,7) 60 (55,6)	16 (23,9) 38 (56,7)	8 (26,7) 16 (53,3)	**59 (21,9)** **147 (54,4)**
Headache	31 (47,7) 19 (29,2)	54 (50,0) 32 (29,6)	31 (46,3) 21 (31,3)	18 (60,0) 7 (23,3)	**134 (49,6)** **79 (29,3)**
Dizziness	37 (56,9) 9 (13,8)	76 (70,4) 12 (11,1)	42 (62,7) 9 (13,4)	18 (60,0) 3 (10)	**173 (64,1)** **33 (12,2)**
Low back pain	25 (38,5) 26 (40,0)	42 (38,9) 46 (42,6)	21 (31,3) 36 (53,7)	9 (30,0) 14 (46,7)	**97 (35,9)** **122 (45,2)**

N= number of students

Pain was the most prevalent among the dental medicine students (63%). The lowest prevalence was found among the students of medicine in English, where 49,2% reported they often or always had pain during menstruations (Table 4). The frequency of pain differed throughout the years, with 6th year students most commonly reporting to have pain and 2nd year students had the lowest percentage of pain stated (data not shown).

Bloating, the second most often reported symptom was most common (around 62%) among the students of medicine in English, and dental medicine. Bloating was reported by 100% of 4th year students and less often by 2nd year students of which 79% expressed bloating as a problem (data not shown).

A change in appetite was the third most common symptom (Table 4). Dispersed over the years it was most often stated in the 4th year of the studies and least commonly reported by 1st year students (data not shown).

About one third of the students often or always experienced headaches during their menstruation, and 45% reported low back pain (Table 4).

A statistically significant positive correlations were found between students reporting pain and all other symptoms, except indigestion / reflux (Spearman correlations, $P<0.001$).

In total about 86% of students reported to have needed pain medication at some point due to menstrual pain. Of these 133 or 49% often or always needed to use medications. The biggest percentage giving such an answer were on the program dental medicine, while participants of the program medicine in English had the lowest percentage for the need of pain medication during menstruation (Table 5). The 6th year students with a prevalence of 91.5% were most prone to use medications and the lowest usage was found among 2nd year students where 83.9% said they used medications for period pain (data not shown).

Approximately 12% stated to have often or always used prescription medication for menstruation pain. The biggest percentage with these answers were found among the students of dental medicine and the lowest number among the students of pharmacy (Table 5). Dispersed over the different years, prescription medications were used by around 30% of the 1st year students, 22 % of the 2nd year students, 13.4 % percent of the 3rd year students, 41% of the students in 4th year, 26.2% of 5th years students and finally and most commonly by 45.8% of the 6th year students (data not shown).

Around 9% of participants had sometimes, often or always experienced side effects from medications taken during menstruation (Table 5). In the different years, any side effects were reported from approximately 21% of 1st year students, 11% of the 2nd year students, 3% in 3rd year, 14% in 4th year, 19% of 5th year and 22% of the students in 6th year (data not shown).

Around 10% of the students sometimes, often or always had to seek medical care related to dysmenorrhea (Table 5). It was most common for the 4th year students where an estimated 32% said they had needed to seek at some point medical care for their menstrual related problems and least often seen with 3rd year students of which 8.6% said they had needed to seek help (data not shown).

Around 50% of students stated they used home remedies sometimes, often or always (Table 5). It was more common for 1st year students where 72.7% said they used home remedies and least likely for the 3rd year student of which 60% reported the use of self-care and home remedies (data not shown).

About a third of students stated that sometimes, often or always they needed to stay at home from school/work due to menstrual pains (Table 5). It was most common for 2nd year students overall, of which 66.1% had at some point needed to stay home from school/work due to menstrual problems and least likely for the 3rd year students where approximately 43% stated to have missed school or work (data not shown).

Table 5. The management of menstrual pain reported by female students of four study programs at University of Split School of Medicine that participated in the study.

	Never or rarely, N (%) Often or always, N (%)				
	Medicine in English	**Medicine in Croatian**	**Dental medicine**	**Pharmacy**	**Total**
Have you ever needed pain medications during menstruation?	21 (32,3) 21 (32,3)	26 (24,1) 58 (53,7)	11 (16,4) 43 (64,2)	9 (30,0) 11 (36,7)	**67 (24,8)** **133 (49,3)**
Did you ever use prescription medication for menstruation pain?	55 (84,6) 5 (7,7)	78 (72,2) 16 (14,8)	51 (76,1) 11 (16,4)	27 (93,1) 1 (3,4)	**211 (78,4)** **33 (12,3)**
Did you ever experience side effects from any drug taken for menstruation pain?	58 (89,2) 5 (7,7)	96 (88,9) 7 (6,5)	62 (92,5) 1 (1,5)	29 (96,7) 1 (3,3)	**245 (90,7)** **14 (5,2)**
Did you ever need to seek medical care due to menstruation pain?	59 (90,8) 2 (3,1)	97 (89,8) 4 (3,7)	58 (86,6) 7 (10,4)	28 (93,3) 1 (3,3)	**242 (89,6)** **14 (5,2)**
Do you use any home remedies / self-care to ease period pains e.g. exercise, heat therapy, herbal remedies etc.	25 (38,5) 28 (43,1)	59 (54,6) 23 (21,3)	30 (44,8) 23 (34,3)	19 (63,3) 8 (26,7)	**133 (49,3)** **82 (30,4)**
Did you ever needed to stay home from school / work due to menstruation pain?	48 (73,8) 7 (10,8)	71 (65,7) 18 (16,7)	38 (56,7) 15 (22,4)	21 (70,0) 3 (10,0)	**178 (65,9)** **43 (15,9)**

N= number of students

Overall, mother/sister was the most consulted person for support with 119 or 45% of all participants stating this. In less percentage (27%) consulted friends and 22% doctors. Six percent of students reported they consulted others, such as teachers or internet or did not consult anyone (data not shown).

The most often used drug for dysmenorrhea and common for all the programs, was NSAIDs (60,4%) with Ibuprofen being the most common choice among the NSAIDs. Four percent reported taking antipyretics and around 2% reported taking contraceptives. About 10% reported to take the combination of drugs, such as NSAIDS and contraceptives, while 2% reported to had taken other types of drugs, such as drugs for spasms (Table 6). Only one student (of dental medicine) named opioid Tramal for her treatment of dysmenorrhea.

The students listed the following medications as most frequently used: Ibuprofen, Diane, Paracetamol, Buscopan, Eveluna, Novalgin, Aspirin, Dolormin, Lekadol, Ketonal.

A significant difference was seen between the types of drugs used for dysmenorrhea and year of the study (χ^2 =55.48, P<0.001). It is worth noting that the trend of not taking the drugs decreased from 1st to final year of the study (46%, in the first year, 32% in 2nd year, 20% in 3rd year, 14% in both 4th and 5th year and only less then 7% in the final year of the study). The NSAIDs use increased with students' age: NSAIDs were used for pain relief by 39% of the 1st year students, 41% of the 2nd year students, 63% of the 3rd year students, 68% of the 4th year, 74% of 5th year students and 71% of the 6th year students.

The antipyretics were used by 4% of students, mostly by 2nd year students (11%). The contraceptives were used only by 2nd (4%) and 6th year students (5%) for dysmenorrhea. The combinations of drugs were mostly used by 6th year students (15%) and the least by 4th year.

The 4th year students reported to use other drugs, such as drugs for prevention of spasms, in the highest number (9%) (data not shown).

Students from medicine in English reported NSAIDs as the most commonly used drug to relieve pain, with Ibuprofen being mentioned as the most common subtype. No students from this program reported the use of opioids.

On the program medicine in Croatian, NSAIDs were again listed as the most frequently used drug to ease pain during menstruation and most common subclass was Ibuprofen. Compared to medicine in English this program also stated Buscopan as the drug of choice.

Dental medicine students reported NSAIDs as the most often used medication to ease pain from menstruations. Paracetamol, OCTs and no drugs were all mentioned in low numbers.

Pharmacy students most often used NSAIDs but the option of no drugs was reported in the highest percentage in this group (Table 6).

Table 6. Types of medications used, and medication practice for dysmenorrhea reported by female students of four study programs at University of Split School of Medicine that participated in the study.

N (%)	Medicine in English	Medicine in Croatian	Dental medicine	Pharmacy	**Total**
No drugs (or non-reported)	18 (27,7)	15 (13,9)	13 (19,4)	10 (33,3)	**56 (20,7)**
Nonsteroidal anti-inflammatory drugs (NSAIDS)	31 (47,7)	74 (68,5)	42 (62,7)	16 (53,3)	**163 (60,4)**
Antipyretics	2 (3,1)	1 (0,9)	4 (6,0)	4 (13,3)	**11 (4,1)**
Contraceptives	1 (1,5)	3 (2,8)	1 (1,5)	0 (0)	**5 (1,9)**
Combination of drugs	10 (15,4)	12 (11,1)	7 (10,4)	0 (0)	**29 (10,7)**
Others	3 (4,6)	3 (2,8)	0 (0)	0 (0)	**6 (2,2)**

N= number of students

More than half of the students reported to have taken the drugs for menstrual pain when needed, while a third took the drugs 1-2 times per day. Only 7% took the drugs for menstrual pain 3-4 times per day. When asked how many days they needed to take the drugs for pain, most of them (93%) stated 1-2 days (Table 7).

Table 7. The frequency and duration of the drug use for menstrual pain of female students of four study programs at University of Split School of Medicine that participated in the study.

	Medicine in English	Medicine in Croatian	Dental medicine	Pharmacy	**Total**
Frequency of drug used per day N, (%)					
1-2 times per day	20 (35,7)	30 (30,3)	24 (36,4)	9 (39,1)	**83 (34,0)**
3-4 times per day	0 (0)	11 (11,1)	5(7,6)	1(4,3)	**17 (7,0)**
When needed	36 (64,3)	58 (58,6)	37 (56,1)	13 (56,5)	**144 (59,0)**
Duration of drug use N, (%)					
1-2 days	50 (92,6)	90 (92,8)	59 (92,2)	23 (95,8)	**222 (92,9)**
3-4 days	3 (5,6)	4 (4,1)	4 (6,3)	1 (4,2)	**12 (5,0)**
5 or more days	1 (1,9)	3 (3,1)	1(1,6)	0 (0)	**5 (2,1)**

N=number of students

5. DISCUSSION

In this study we investigated the prevalence and management strategies of dysmenorrhea among the female students at the University of Split School of Medicine, of four study programs: medicine in English, medicine in Croatian, dental medicine and pharmacy.

The mean age of the participants was 23 years with minimum of 18, and maximum being 30. In their study from 2011, researchers at the department of Obstetrics and Gynecology, Institute of Clinical Sciences, at Gothenburg University concluded that increasing age reduced the severity of dysmenorrhea (79). Further studies have shown that primary dysmenorrhea tends to decrease with age, especially after 30 (80).

The mean age of menarche was estimated to 13 years ranging from 6-17, a number in accordance with previous studies which found the average age of menarche to be 13.8 ± 1.6 years (81). Several studies have shown an association between dysmenorrhea and an early age of menarche (82). A reason for this could be the prolonged exposure to prostaglandins.

When asking about the use of contraceptives, an overall total of 26% said they were using contraceptives. There was a significant difference between the different programs, with the highest percentage of use being found among the students of medicine in English, where almost half of students stated the use of contraceptives compared to 13% of the pharmacy students.

The numbers from the pharmacy program are in agreement with the prevalence reported in a study that compared the practice of oral contraceptives among 4043 female students in Spain, which found that 14.42 % of the adolescents and young women living in Spain had been using oral contraceptive pills in the last two weeks leading up to the survey (79). The significantly more prevalent use among the students of medicine in English could be attributed to differences in customs and tradition regarding contraceptives.

The majority of the students (68%) reported that their menstrual bleeding lasted for 5-7 days, 28% of students said that they had less than 5 days of bleeding, while only 4% reported more than 7 days. These numbers match the reported duration from the cross sectional study at King Khalid University in Saudi Arabia, where the average number of bleeding days per cycle was found to be 6.3 ± 1.2 days, with a range of 2–9 days and most of their respondents (83.2%) reported 5–7 bleeding days per period (83).

There is a statistical difference between the days of bleeding reported from different studies, with most of the medical studies in Croatian, dental and pharmacy students reporting 5-7 days, and medical studies in English students mostly reported <7 days. This could possibly be explained by the fact that students of the English speaking medical program used

contraceptives in much higher number, which is knows to affect the duration and amount of menstruations (85).

Amidst the 270 participants, 17% reported to never or rarely have experienced pain during menstruation while 25% reported to sometimes experience pain and 58% reported they often or always experienced pain with their menstrual cycles. These numbers are in accordance with the prevalence rate reported by De Sanctis and El Kholy who did a review of 50 studies and found the prevalence rate of dysmenorrhea ranging from 67% to 90% for those aged 17-24 years (2) Slightly different prevalence rate of dysmenorrhea was reported by researchers from Dumlupinar University in Western Turkey, 72.7% among its 623 female students. One reason for the variation could be the selected groups of women where age differed between the high school students and university students and the absence of a universal method of defining dysmenorrhea (78).

Pain often or always was most prevalent among the dental students and the students of medicine in Croatian, where 63% and 61% respectively, stated this. On the program medicine in English 49% of the students said they had pain often or always and among the pharmacy students 54% said they often or always had pain. These findings differ from those reported from a cross-sectional study conducted at the College of health science in KKU, Saudi Arabia, where 36% of the female students were found to have severe pain. The different results may be due to differences in methodology and definition of severe pain (83).

Again, the higher prevalence of pain reported by students of medicine in Croatian and dentistry may be attributed to the fact that these the same two programs reported the highest occurrence of pelvic pathologies, with 24% of students at medicine in Croatian and 24% of students on the dental medicine program, compared to 12% of the students on medicine in English and 10% of pharmacy students.

The consequences of pain force many women to use medications in order to relieve their menstrual cramps. When investigating pain management methods of the participants we found that the majority of the students (49%) often or always had to use analgesics for pain management. A quarter of students said they never or rarely had to use medication for their pain, and the same percentage reported to have used these medication “sometimes”. In certain Middle eastern countries like Palestine, approximately 58% of the students with dysmenorrhea opted for pain relief medications during their menstrual periods (84).

The students of medicine in Croatian and the students of dentistry had most students which stated that they often or always took medications for dysmenorrhea. Again this could be

attributed to the aforementioned findings, that these two study programs had the highest prevalence of both pain and pelvic pathologies.

The most frequently used drug to ease painful menstruation, across all programs and all study years was NSAIDs, with an estimated 60% using some form of NSAIDs of which the biggest subclass was ibuprofen (31%). These results were of no surprise since many previous studies have consistently concluded that around 58% to 70% of girls tend to self-medicate with non-steroidal anti-inflammatory drugs and analgesic medicine for dysmenorrhea (57).

Another parameter that further highlights the prevalence of dysmenorrhea is the overall 16% of students that said they always had absenteeism from school due to pain during menstruations. These numbers are higher than those obtained from studies about dysmenorrhea and its effects on school absenteeism among adolescent girls in selected secondary schools in Ibadan, Nigeria, which reported that 13% of their students had missed school due to dysmenorrhea (8). The highest percentage, 22.4% was among the students in the program of dental medicine which reported they often or always needed to be absent from school or work due to painful menstruation. These students also had the highest prevalence of severe pain during their menstrual cycles, which could be a reason for them most often needed stay home from school.

There were certain limitations with the study, mainly due to a limited sample group. The results should not be generalized since certain study years and programs were represented in higher numbers. The study was first planned as a questionnaire that would be distributed in the classroom which would have increased the number of participants. Secondly, due to the online format it was not possible to answer any questions the participants might have had regarding the questions. In addition, when self-reporting on menstrual problems, bias cannot be ruled out. A final limitation of the present study is the lack of a universal defining criteria for dysmenorrhea.

6. CONCLUSION

In conclusion the study shed light on the high prevalence of dysmenorrhea among this study group and that it does have an impact on school absenteeism. Self-medication with analgesics, mainly non steroid anti-inflammatory medications is the most common way to deal with the menstrual pain among our study group.

It is evident that even with the use of pharmacological and non-pharmacological methods, many students struggle to control their pain at a satisfactory level. To support and assist female students with their menstrual pain is of great important and could have a positive outcome on school absence and performance.

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8. SUMMARY

Objectives: The aim of our study is to investigate the impact, prevalence and management of dysmenorrhea among female students of medical studies in English, medical studies in Croatian, dental medicine and pharmacy students at University of Split School of Medicine.

Materials and methods: A cross-sectional study was carried out amongst the female students of four study programs: Medical studies in Croatian, Medical studies in English, Dental medicine and Pharmacy, enrolled at University of Split School of Medicine in Split, Croatia. All female students enrolled into one of the four studies were eligible as participants in this study. The questionnaires were administered to students of all academic years (1 - 6 for medical studies and dental medicine, and 1 - 5 for pharmacy), in online version created in Google Docs during the period of three months, from April until June of 2020. The participation was voluntary, anonymous and without compensation. A total of 273 female students, out of 858 enrolled at University of Split School of Medicine participated in this study.

Results: The mean age of the participants was 22.8 (SD± 2,1), with minimum of 18, and maximum being 30. First year students were 19 years old on average, second year students 20, third year students 21, fourth year students 22, fifth 23 and sixth 24 years old.

Among the participants about 98% of students reported to have some kind of menstruation associated symptoms (problem graded >2 on the scale). The most frequent symptom was pain and the least common was vomiting. For problems that occurred often or always about 58% of students stating to have experienced pain, 11% nausea, 2% vomiting, 56% bloating, 16% reflux, 54% change in appetite, 29% headache, 12,2% dizziness and 45% lower back pain.

The most often used drug overall and common for all the programs, was NSAIDs (60,4%) with Ibuprofen being the most common choice. Ten percent reported to taking the combination of drugs and 20.7% did not report or they stated they were not taking any drugs for menstrual pain.

First year students of all programs most commonly used NSAIDs for pain relief, 2nd year students the highest usage of oral contraceptives, in 3rd, 4th and 5th year NSAIDs were most often used to ease the pain. The use of NSAIDs increased with years of the study. The combinations of drugs were mostly used by the 6th year students.

Conclusion: This study confirmed that dysmenorrhea is a problem of large magnitude among female students. Furthermore, the most used management strategies include use of non-steroid anti-inflammatory drugs, mainly Ibuprofen.

9. CROATIAN SUMMARY

Naslov: Prevalencija, impakt i menadžment dismenoreje među studenticama Medicinskog fakulteta Sveučilišta u Splitu

Cilj: Cilj ovog istraživanja bio je ispitati utjecaj, prevalenciju i upravljanje dismenorejom među studenticama medicine engleskom i na hrvatskom jeziku, studenticama dentalne medicine i farmacije Medicinskog fakulteta Sveučilišta u Splitu u Republici Hrvatskoj.

Materijali i metode: U ovom radu napravljeno je transverzalno istraživanje među studenticama četiri studijska programa Medicinskog fakulteta Sveučilišta u Splitu: medicina na engleskom i hrvatskom jeziku, dentalna medicina i farmacija. Sve studentice upisane na bilo koji od navedenih studija bile su prihvatljive kao sudionici ovog ispitivanja. Upitnici su poslani studenticama svih akademskih godina (1 - 6 za medicinu i dentalnu medicinu, a 1 - 5 za studij farmacije), u online verziji stvorenoj u Google dokumentima u razdoblju od tri mjeseca, od travnja do lipnja 2020. Sudjelovanje je bilo dobrovoljno, anonimno i bez naknade. U ovom istraživanju sudjelovale su ukupno 273 studentice, od 858 upisanih na Medicinski fakultet Sveučilišta u Splitu.

Rezultati: Srednja dob sudionica iznosila je 22.8 (SD ± 2,1), minimum 18, a najviše 30. Studentice prve godine imale su u prosjeku 19 godina, studenti druge godine 20, studenti treće godine 21, studenti četvrte godine 22, pete 23 i šeste 24 godine.

Oko 98% studentica navelo je da ima neki od simptoma povezanih s menstruacijom (problem ocijenjeno >2 na ljestvici). Najčešći simptom bila je bol, a najmanje čest povraćanje. Za probleme koji su se javljali često ili uvijek oko 58% studentica navelo je bol, 11% mučninu, 2% povraćanje, 56% nadutost, 16% refluks, 54% promjenu apetita, 29% glavobolju, 12.2% vrtoglavicu i 45% bol u donjem dijelu leđa.

Najčešće korišteni lijekovi među studentima svih studija bili su nesteoridni protuuplani lijekovi, NSAIL (60,4%) i to ibuprofen kao najčešći izbor. Deset posto studentica uzimalo je kombinaciju lijekova, a 20.7% nije navelo lijekove ili su izjavili da nisu uzimali nikakve lijekove za menstrualnu bol. Studentice prve godine svih studija najčešće koriste NSAIL, kao i studentice treće, četvrte i pete godine. Studentice druge godine u najvećem postotku su uzimale oralne kontracepcijske pilule. Primjena NSAIL-ova povećala se s godinama studija. Kombinacije lijekova uglavnom su koristile studentice 6. godine.

Zaključak: Ovo istraživanje potvrdilo je da je dismenoreja značajni problem među studenticama. Najčešće korištene strategije upravljanja uključuju korištenje nesteroidnih protuupalnih lijekova, uglavnom Ibuprofena.

10. CURRICULUM VITAE

Personal information

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Address:	Katarina Bangata 50, 11639, Stockholm
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Education:

2014-2020 University of Split School of medicine, Split, Croatia.

2013-2014 University of East London, London.

2010-2011 Albion College, London

Clinical work experience:

01/2020 – Clinical Observer, Barnet & Chase Farm Hospital department of Gynaecology & Obstetrics, London

12/2019 – Clinical Rotation, Karolinska Institutet Department of Gynaecology & Obstetrics, Stockholm

09/2017 – Clinical research observer, Bioengineering Sahlgrenska University Hospital, Gothenburg

Work experience:

10/2012 – 7/2013 Supervisor, Nomad Travel Clinic & Travel Store, London

09/2011 – 08/2012 Sales consultant, Selfridges, London

Extra-curricular:

09/2019 - First Aid Provider, FAST – First Aid Support Team, Calais, France

08/2018 - Medical Assistant, Med Equali'Team, Samos, Greece

2010 - Volunteer in homeless shelter, Shelter from the storm, London

2006 – Work experience, Karolinska University Hospital, Swede

Additional qualifications:

08/2017 – Combat Medic / EMT-Basic, Aalborg, Denmark

08/2017 – Tactical Emergency Causality Care, Aalborg, Denmark

08/2017 – Basic Military Provider Course, International Trauma Life Support, Aalborg, Denmark

Languages:

Swedish (mother tongue)

English (C1)

French (B1)

11. SUPPLEMENT

INSTRUCTIONS:

The questionnaire in front of you is a part of a scientific research in which we want to examine the impact and management of dysmenorrhea among students of medicine, dental medicine, pharmacy and medical students in English.

The questionnaire is completely anonymous. All the information provided in the questionnaire will be used exclusively for scientific purposes, and the identity of the participants will be completely anonymous for both researchers and the public. In this questionnaire, you will not be asked to provide your name and surname at any time. So please answer the questions fairly and openly.

You will need about 10 minutes to complete this questionnaire.

General information:

Please answer the following questions:

1. Age: _____ (Write in)
2. Study program: Medicine / Dental medicine / Pharmacy / Medical studies in English
3. YEARS OF STUDY: 1. / 2. / 3. / 4. / 5. / 6.
4. Age of the first menarche _____
5. Use of contraceptives YES / NO
6. Do you have any history of pelvic pathologies YES / NO
7. Menstrual cycle (circle) _____REGULAR / IRREGULAR _____

Character of menstruation

Please circle the category that best shows your character of menstrual cycle within the following statements:

Duration of menstrual cycle (days)	<28	28-35	>35
Days of menstrual bleeding	<5	5-7	>7
Menstrual flow	Light flow	Medium flow	Heavy flow

Please circle the number that best shows your agreement or disagreement with the following statements:

(1 = never, 2= rarely, 3= sometimes, 4= often, 5=always)

Have you ever experienced the following associated symptoms?

Pain	1	2	3	4	5
Nausea	1	2	3	4	5
Vomiting	1	2	3	4	5
Bloating	1	2	3	4	5
Indigestion/reflux	1	2	3	4	5
Change in appetite	1	2	3	4	5
Headache	1	2	3	4	5
Dizziness	1	2	3	4	5
Low back pain	1	2	3	4	5

Management of menstrual pain

Have you ever needed pain medications during menstruation?	1	2	3	4	5
Did you ever use prescription medication for menstruation pain?	1	2	3	4	5
Did you ever experience side effects from any drug taken for menstruation pain?	1	2	3	4	5
Did you ever need to seek medical care due to menstruation pain?	1	2	3	4	5
Do you use any home remedies / self-care to ease period pains e.g. exercise, heat therapy, herbal remedies etc ?	1	2	3	4	5
Did you ever needed to stay home from school / work due to menstruation pain?	1	2	3	4	5

Persons consulted for dysmenorrhea (menstrual pain) (please circle your answer):

Friends / Mothers/sisters / Doctors / Teacher

Types of medications used, and medication practice (please circle the type of drug or combination of drugs):

No drugs / Antipyretics / Nonsteroidal anti-inflammatory drugs (NSAIDS), such as aspirin / Opioids /Contraceptives

Name of the drug used (most often):_____

Frequency of drug used per day	1-2 times per day	3-4 times per day	when needed
Duration of drug use	1-2 days	3-4 days	5 or more days