Demystification of All Too Common Disease: Period Pain

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What is the mechanism of menstrual pain-alleviating medicines?
How can we guide research pathways to treat menstrual pain?

Abstract

The prevalence of menstrual pain is high yet there is a lack of research and understanding of it. There are three main categories of menstrual pain-alleviating medicines that are commonly prescribed: NSAID (Non-Steroidal Anti-Inflammatory Drugs), acetaminophen and oral contraceptive pills. Two of these types of drugs are broad pain alleviators whereas oral contraceptive pills play a role specifically within reproductive organs. Much research has been dedicated to understanding the biochemistry of the mechanisms of these medicines and how pain is generated at a molecular level. Genetics vary from human to human and can also play a role in menstrual pain and its alleviating methods. So far, some research efforts have focused primarily on menstrual pain, but most people who experience pain have little access to information on how pain alleviation works, what the source of menstrual pain is, and what ongoing efforts could be made to improve the quality of life. I argue that future research should focus on menstrual pain specifically and how to alleviate it with more targeted therapies. These broad efforts will enhance our understanding of reproductive health sciences and have a significant impact on a large portion of the human population.

Language Disclaimer

This document will refer to ‘women’ or ‘females’ as biological females who are born with XX chromosomes and female reproductive organs only. When discussing others, such as transgender women or intersex individuals, it will be specifically indicated as ‘transgender women’ or ‘intersex’.

Introduction

Roughly 3.2 billion females “experience period pain at some stage in their lifetime” [1]. However, painful menstrual cycles are not normal, and in fact point to underlying disease. Period pain, often referred to in medical literature as dysmenorrhea, is broadly defined as pain associated with any stage of the menstrual cycle, which occurs cyclically throughout the majority of a biological female’s life from puberty to menopause [2]. Dysmenorrhea is therefore considered a chronic health issue but is very poorly defined, and needs to be addressed with much more basic scientific and medical research in order to address. Our current understanding and the treatments for chronic diseases are lacking due to the chronic diseases’ relatively benign characteristics when compared to detrimental health issues such as cardiac problems, cancer, and more. Chronic pain is “long-standing pain that persists beyond the usual recovery period or

occurs along with a chronic health condition" [3]. I argue that addressing the root causes and fully treating dysmenorrhea will set the stage for a vast overhaul of our current approaches in the medical world towards treating all conditions, not just acute ones. Because dysmenorrhea affects so many people, the outcomes of treatment will have far-reaching effects. For example, pain reduction would impact the daily lives of billions of people suffering from this currently untreated disease. To achieve equality and equity between the sexes and to endorse an advanced medical care system, there must be constant attention and effort to research in the area of women's health sciences.

Dysmenorrhea is defined as "pain during the menstrual cycle", located in the lower abdomen and may also encompass other symptoms such as back pain [4]. There are two types of dysmenorrhea: primary dysmenorrhea which occurs from the menstruation process and secondary dysmenorrhea which originates from "existing pelvic conditions" such as endometriosis [5]. The menstrual cycle is a critical factor in female health; not only does it function to release eggs but it also regulates the overall physical and psychological health of females. As a result, many symptoms are associated with menstruation. Surprisingly, most of the biological details of how the reproductive system works are still veiled to most people. When compared to other diseases, dysmenorrhea lacks enough mechanistic study to adequately propose effective treatments.

Statistics that correlate menstrual pain and socioeconomic outcomes advocate for improved treatments for dysmenorrhea. A study revealed that "an average productivity loss of 33% resulted in a mean of 8.9 days of total lost productivity per year" due to menstrual health-related conditions [6]. The suffering from an abnormal condition happens regularly for normally menstruating biological females on a monthly basis. Furthermore, dysmenorrhea not only consists of physical pain but also psychological suffering as well. Dysmenorrhea and psychological conditions have been correlated by a study and the data shows that there is a statistical significance between them [5]. A medical condition that has physical and psychological consequences on people affects society as a whole and socioeconomics in the end.

Dysmenorrhea is one of the most promising chronic conditions to invent a solution for as it stems from the menstrual cycle, a normal biological process that can be studied in a variety of ways. Menstrual cycles are evolutionarily conserved among mammals, and it has the potential to be well understood with the right research efforts. Currently, common pain alleviators and oral contraceptive pills are the most common recommendations from gynecologists, but no targeted treatment method has been proven to be highly effective for the majority of biological females.

There is much more to be explored in the study of female reproductive health. Recent studies have shown that there is a statistical significance in the correlation between dysmenorrhea and genetic factors [5]. Understanding the underlying genetic factors that impact female reproductive health will provide a deepened understanding of the condition itself and improve the development of treatments as well.

In this work, I will be demystifying period pain and stress dysmenorrhea as an abnormal health condition, strongly urging the research community to shift focus toward period pain as a true

chronic illness, like all chronic illnesses, that needs systematic research focus to address. This document encompasses a literature review of the current methods existing to treat dysmenorrhea, and it describes the molecular details of how currently prescribed medications work and their pitfalls. Moreover, the document highlights missing information in women's health sciences that needs to be acquired to improve women's health technologies and knowledge.

Background: Dysmenorrhea is a disease of the menstrual cycle

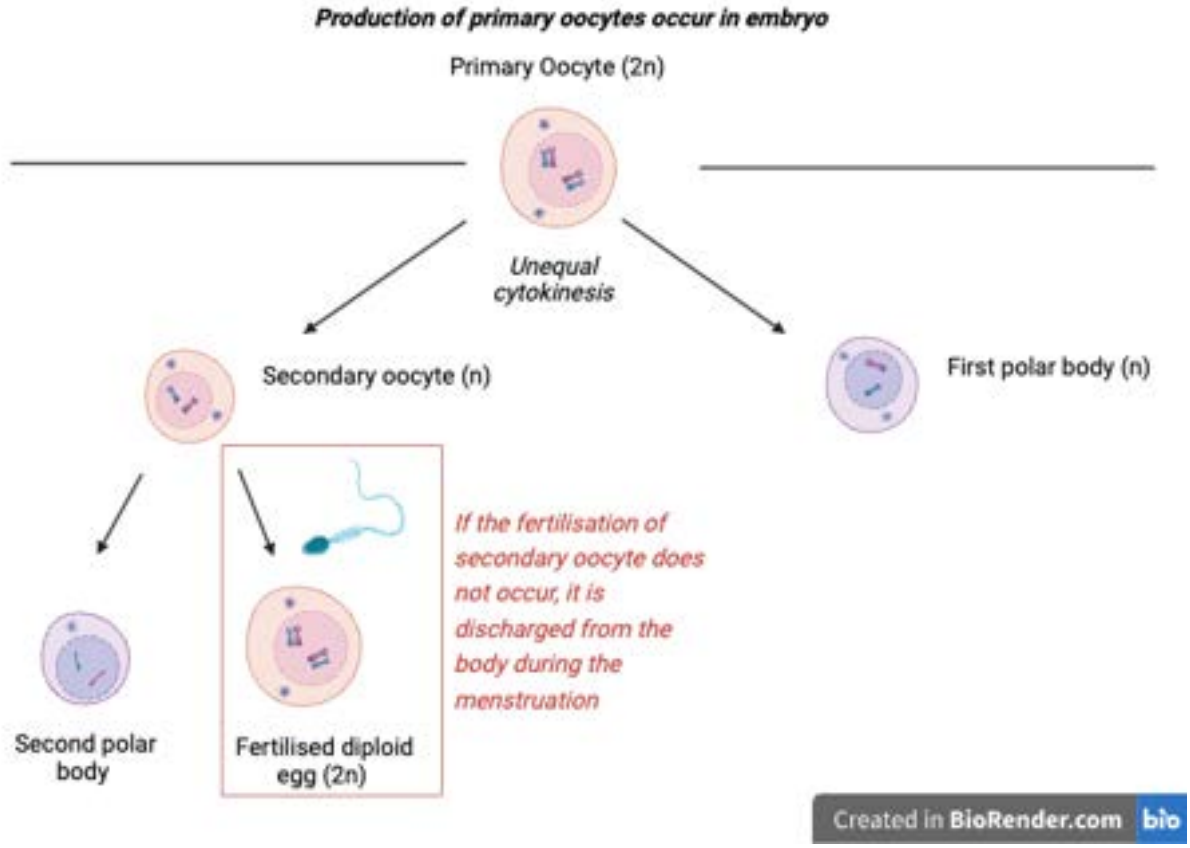

Figure 1. A diagram of oogenesis. Created with BioRender.com.

Every biological female is born with a certain amount of primary oocytes, which eventually develop into mature eggs [7]. In a female embryo, as the ovary is developing, mitosis produces many primary oocytes [10]. The number of oocytes that are produced in this process determines the total amount of oocytes the individual can release in their lifetime [10]. However, only a subset of oocytes enter the maturation process and are released [10]. Every primary oocyte has completed meiosis I and is at the onset of meiosis II [10]. When an adolescent female reaches puberty, then meiosis II begins; thus, they become fertile [10]. The secondary oocyte is arrested at the metaphase stage of meiosis II [10]. The secondary oocyte is released from one of the ovaries (see Figure 1) each month and it is either fertilised by a sperm or released from the

body with the lining (endometrium) of the uterus along with broken down blood vessels and blood [10]. Therefore, the purpose of the menstrual cycle is to release the mature secondary oocyte that has completed meiosis into the uterus. If the mature oocyte (egg) is not fertilized, it is released along with extraneous materials (lining, blood, and unfertilised ovum) from the body [10]. Otherwise, pregnancy occurs [10].

The menstrual cycle is a natural part of reproduction as an animal [10]. Although not all mammals go through the menstrual cycle, many do go through a similar cycle called the estrous cycle [11]. While the cycle itself is a natural phenomenon, dysmenorrhea is an abnormal health condition that imposes abdominal pain and other symptoms. As an analogy, in intestinal obstruction, a well-functioning organ is disrupted. In dysmenorrhea, the functioning of reproductive organs is disrupted. When compared to other abnormal health conditions, dysmenorrhea is especially considered to be a natural part of the reproductive cycle instead of a diseased state. Thus, dysmenorrhea should be viewed as a disease of the menstrual cycle, not a naturally occurring part of the menstrual cycle, and treated medically as such.

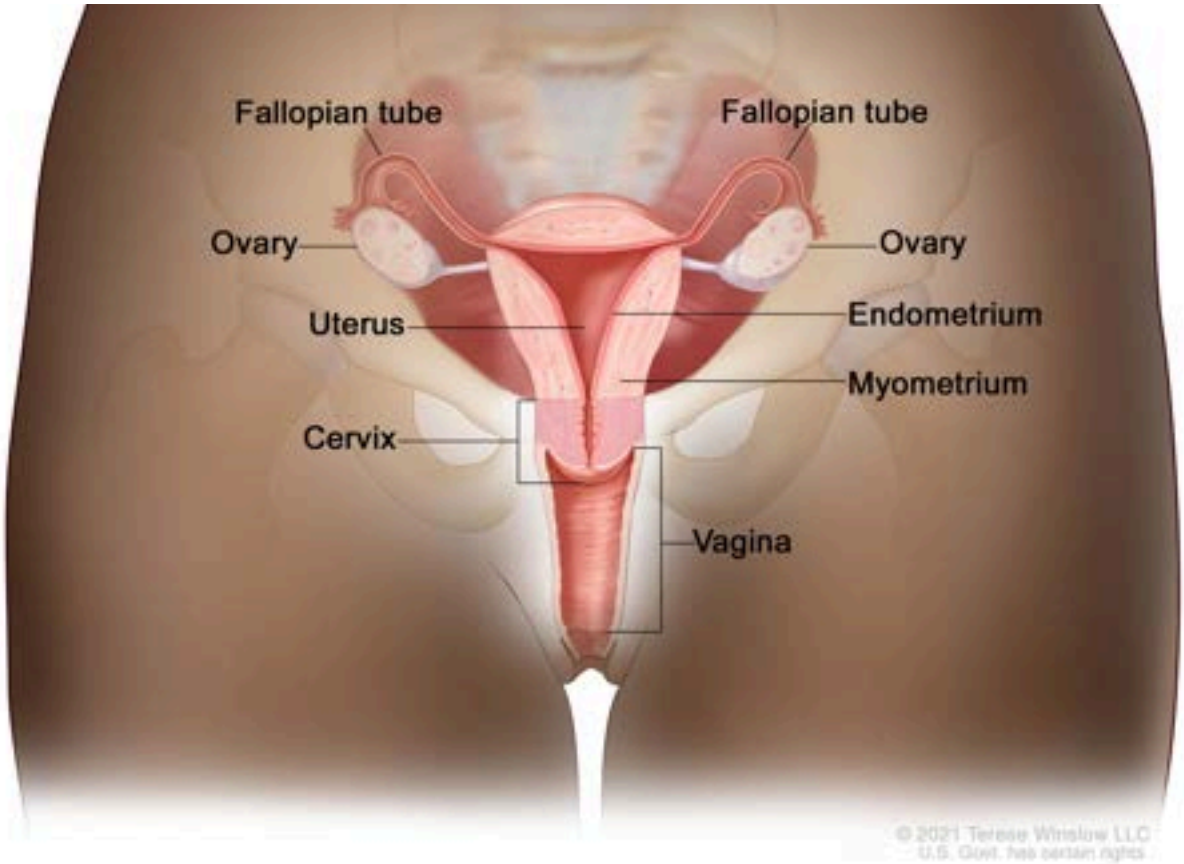

Figure 2. A diagram of female reproductive systems [8].

Figure 3. A diagram of the menstrual cycle with a visual representation of the endometrium layer [9].

The menstrual cycle is a monthly cyclic process (28 to 35 days pattern) of shedding the lining of the uterus [9, 10]. Driven by hormones, there are 4 phases within the menstrual cycle: The menses phase (menstruation), the follicular phase (proliferative phase), ovulation, and the luteal phase (secretory phase) [9].

1. Menstruation
   The phase begins on the first day of “the period” when the bleeding occurs. The shedding of the lining of the uterus occurs when the individual is not pregnant. It typically lasts from three to seven days.

2. Proliferate phase
   The proliferate phase overlaps with menstruation and ovulation. It begins on the first day of menstruation and ends at ovulation. The female main sex hormone estrogen fluctuates and other hormones cause follicles in the ovaries to grow. Within days 10 to 14 of the menstrual cycle, one of the follicles will form a fully mature egg, an ovum.

3. Ovulation
   The ovary releases the egg. The phase lasts from day 14 to 28.

4. Secretory phase
   The egg is secreted and travels down the tubes from the uterus. The progesterone level increases to help prepare for the body to be pregnant. When the egg is not fertilized by the sperm, the egg is released along with the lining of the uterus in the menstruation phase. This phase lasts from day 15 to 28.

There are two types of dysmenorrhea: primary and secondary [5]. First, primary dysmenorrhea occurs from the contraction of the uterine muscle [5]. Prior to menstruation, linings start to form on top of the uterus muscles [12]. Lining is a condensed form of menstrual blood and it is harder to excrete than to excrete liquid blood [12]. Subsequently, the uterine muscles need to contract much more to excrete the lining. Second, secondary dysmenorrhea occurs from diseases such as endometriosis, PCOS, and uterine fibroids [1, 5]. Endometriosis is the formation of tissue outside of the uterus [8]. The lining is shed every month during menstruation and causes pain,

inflammation, and scarring. PCOS may affect the menstrual cycle in various ways; it increases the level of androgens and creates small cysts in the ovaries [5]. An imbalance of hormone levels may cause painful dysmenorrhea [13]. Uterine fibroids are benign smooth muscle tumours of the uterus and the increased amount of shedding affects the contraction of the muscles and leads to more painful dysmenorrhea [5].

1. Biochemical mechanisms of pain treatments for dysmenorrhea

1.1 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) are types of pain alleviators that can reduce inflammation and lessen minor pain [14]. They are commonly prescribed or recommended to treat headaches, toothache, fever, dysmenorrhea, and more. NSAIDs include common nonprescriptions such as Aspirin, Ibuprofen, Naproxen, and Diclofenac.

NSAIDs alleviate pain by inhibiting the production of prostaglandin (PG), a fat molecule implicated broadly in pain sensations such as fever and inflammation via enzyme inhibition [14]. Many hormones and signalling molecules in the body—including PGs—are actively produced inside of cells [14, 15]. A low accumulation of PG is always present in the human body [16]. What causes the pain is the high levels of PG produced in response to injury, not the presence of PG itself [16].

An enzyme is a broad class of globular proteins that act as a biological catalyst, which speeds up the biochemical reactions without being absorbed in the product [17]. In other words, it aids the production of the molecules, such as the PG. A substrate is a reactant in enzyme-catalyzed reactions.

Every enzyme has an active site, the region on the surface of the enzyme where the substrate molecules bind to [17]. The active site and the substrate complement each other, in terms of both shape and chemical properties [17]. Therefore, only certain substrates can bind to a specific enzyme.

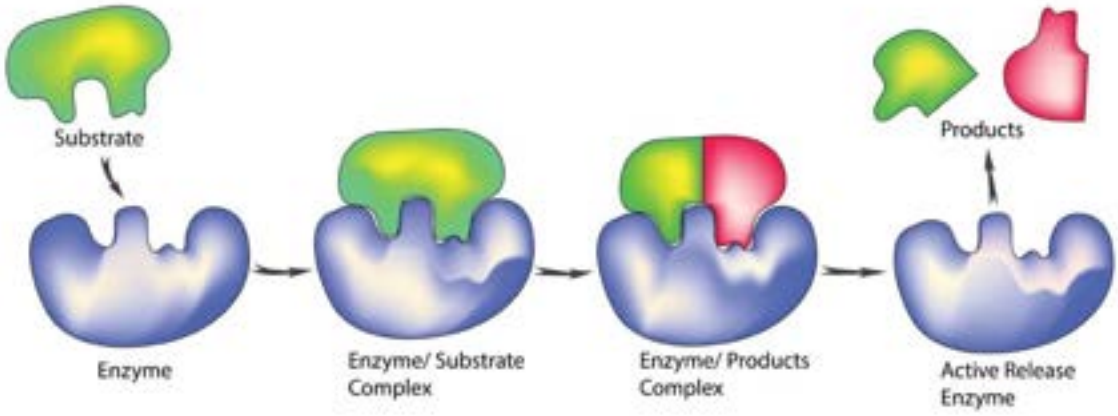

Figure 4. A diagram of enzyme-substrate complex formation [18].

In the case of PG, prostaglandin is the product of the reaction. The reactant, arachidonic acid, binds to the cyclooxygenase (COX) enzyme and produces prostaglandin H_2 (PGH_2) [16]. In this process, NSAID molecules block the formation of the enzyme-substrate complex by binding itself to the COX enzyme [14, 16]. When NSAIDs are bonded to the COX enzyme, arachidonic acid can no longer bind with the enzyme [14, 16]. Thus, when consumed, NSAIDs reduce the rate of PG production, which in turn decreases the production of pain signals in the body [16].

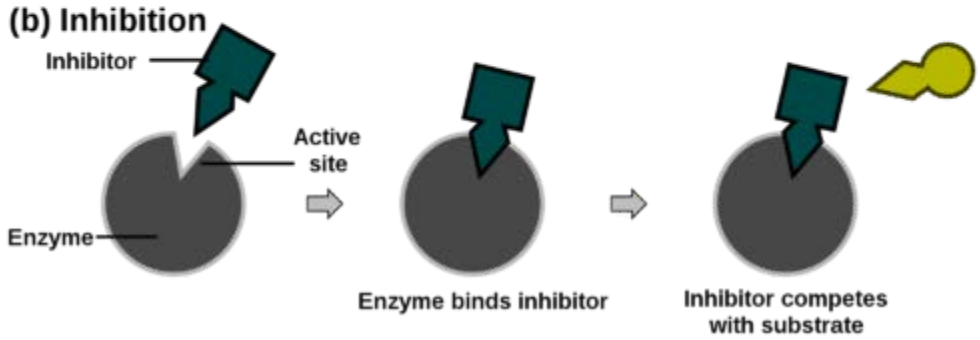

Figure 5. A diagram of enzyme expression inhibition [19].

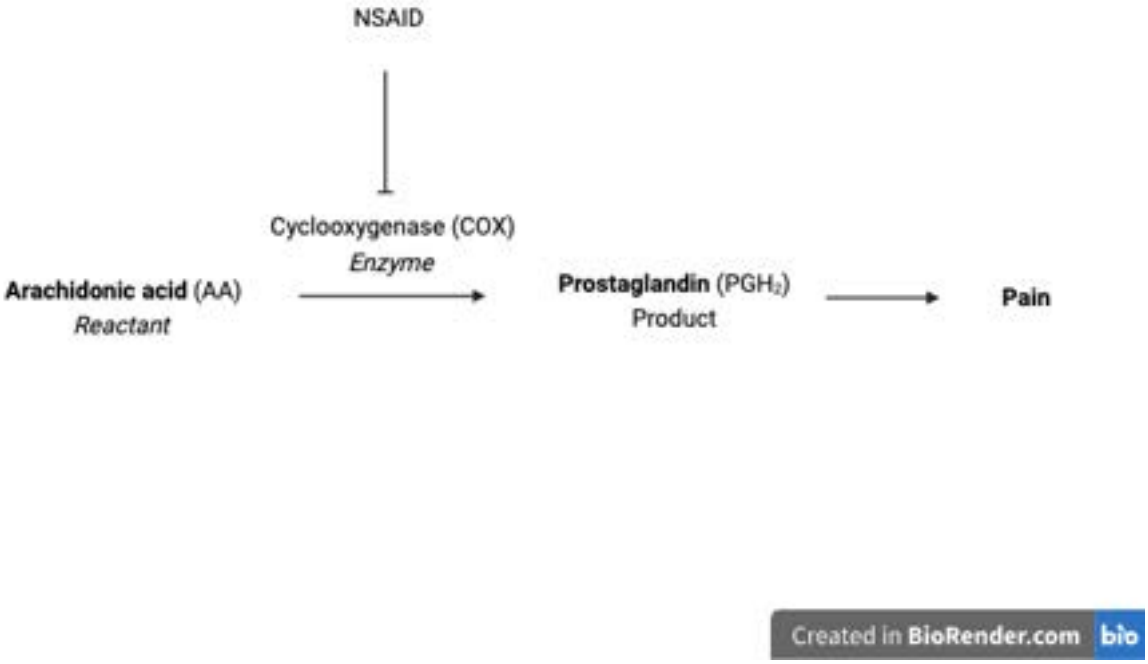

Figure 6. A diagram of the COX inhibition method via NSAID. Created with BioRender.com.

As seen in Figure 7, PGH_2 is converted into various isoforms to fulfill unique functions in designated tissues.

Looking at the prostaglandin's production sites, I propose that prostaglandin F2 alpha could be the origin of menstrual pain because all the other locations of the prostaglandin do not correlate with the menstrual pain. Moreover, prostaglandin F2 alpha is mainly produced from the female reproductive system and plays a critical role in "ovulation, luteolysis, contraction of uterine smooth muscle and initiation of parturition" [20]. See Table 1 for a summary of which prostaglandins affect other organs and tissue types.

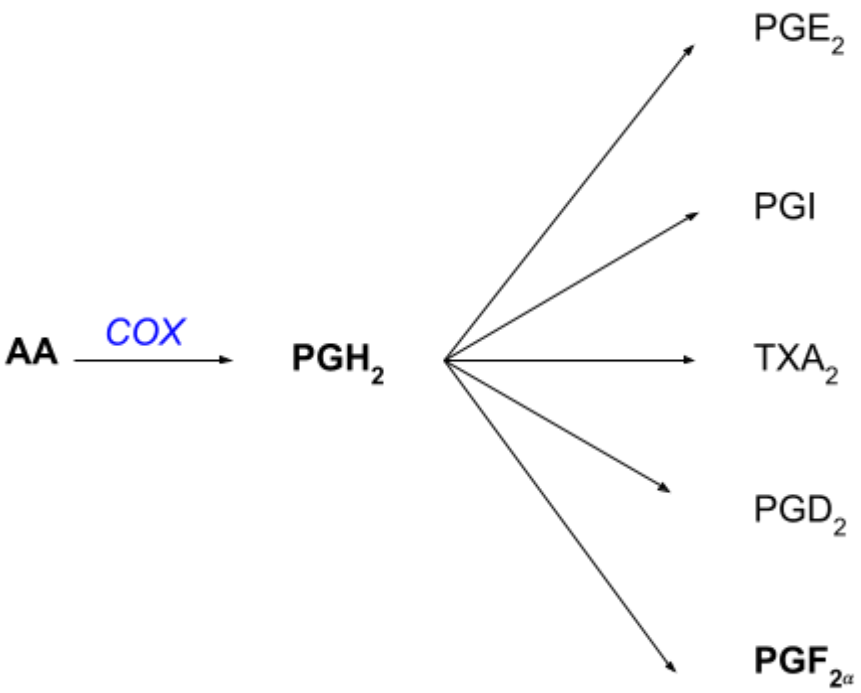

Figure 7. A diagram of prostaglandin and its isoform production.

Name	Location	Function
Prostaglandin E_2	Brain, kidneys, vascular smooth muscle cells, platelets	Regulation of immune responses, blood pressure, gastrointestinal integrity, and fertility. Closely related to the process of inflammation.
Prostacyclin	Endothelium, vascular smooth muscle cells, platelets, kidneys, brain	Regulate cardiovascular homeostasis.
Thromboxane A_2	Platelets, vascular smooth muscle cells, macrophages, kidney	Unstable arachidonic acid metabolite that only lasts approximately 30 seconds.
Prostaglandin D_2	Mast cells, brain, airways	Function in both an inflammatory and homeostatic capacity. Regulate sleep and other central nervous system, including pain reception.

Prostaglandin $F_{2\alpha}$	Uterus, airways, vascular smooth muscle cells, eyes	Involved in ovulation, luteolysis, contraction of uterine smooth muscle and initiation of parturition.

Table 1. Isoforms of prostaglandin and their locations and their functions [20].

Currently, there are two types of COX enzymes known: COX-1 and COX-2 [14, 16, 20]. While COX-1 enzymes are always expressed in most cells, COX-2 is expressed when inflammatory stimuli are induced [14, 16, 20]. Furthermore, COX-2 is the major source of inflammatory prostaglandin production [16, 20]. Thus, pain signals via PGs are typically felt acutely when there is an increase in COX-2-mediated production of inflammatory PGs [16, 20]. NSAIDs are non-selective inhibitors of the COX enzymes, meaning that the drugs inhibit both types of enzymes [14]. Nevertheless, each drug tends to inhibit a certain type of COX enzyme more than the other [14].

Figure 8. NSIAD inhibition method illustration. Created with BioRender.com.

Aspirin inhibits the expression of the COX enzymes by destroying them [14]. Aspirin covalently modifies the COX enzyme, blocking the attachment of the arachidonic acids, and permanently

destroying the enzymes [14]. All other types of NSAIDs except for aspirin are reversible inhibitors of the COX enzymes: they attach themselves to the COX enzyme [14].

1.2 Acetaminophen

Acetaminophen is more commonly known by its brand name Tylenol. Even with a long history as a common pain alleviator, the precise biochemical mechanism of pain relief by acetaminophen has not been determined [21]. It is a type of pain alleviator that acts similarly to the NSAIDs in our body but lacks its effect in reducing inflammation [21]. It is possible that acetaminophen can reduce fever and increase the pain threshold for painful stimuli by inhibiting the expression of the COX enzymes [21]. Thus, acetaminophen aids in alleviating menstrual pain by increasing the pain threshold.

Some studies have suggested the existence of a COX-3 enzyme which is suspected to be a variant of COX-2 mainly produced in the lung with different molecular characteristics, which may be targeted by acetaminophen [21]. The mechanism of acetaminophen is similar to that of NSAIDs; however, it is shown that acetaminophen is less able to inhibit the expression of the COX enzymes when the concentration of cellular peroxide, which is produced from inflammation, increases [21]. Therefore, while acetaminophen is useful as a pain alleviator, its exact biochemical pathway is not well understood.

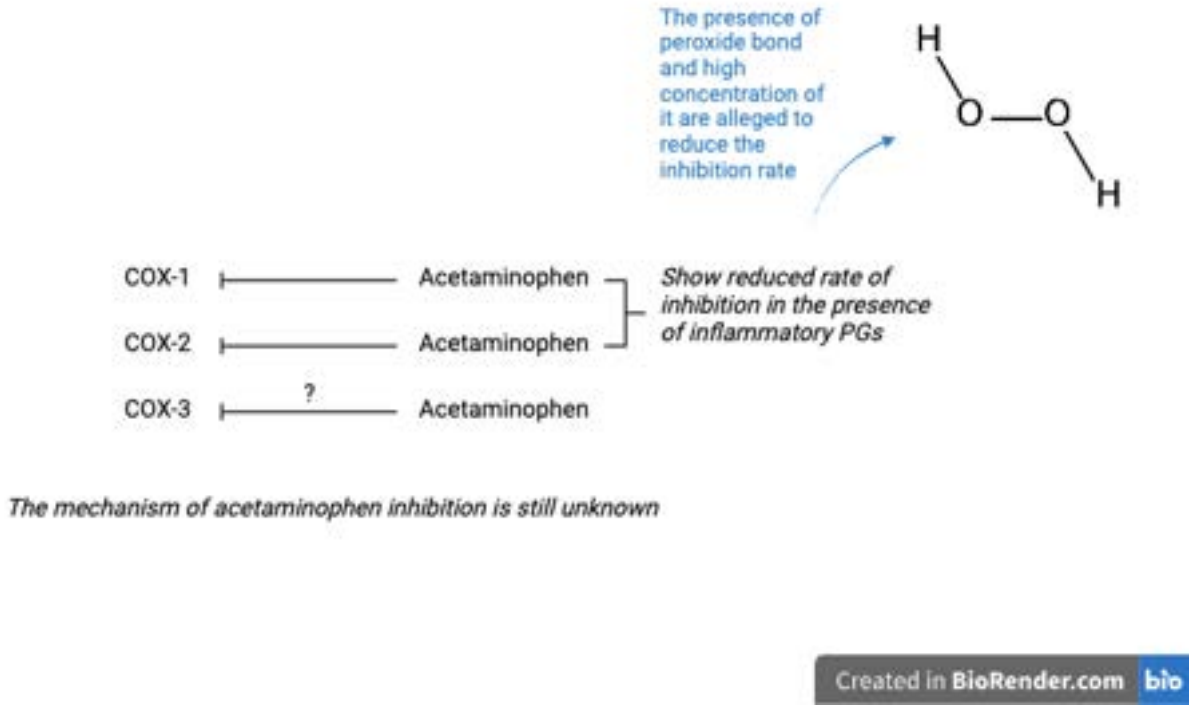

Figure 9. COX enzyme inhibition by acetaminophen. Created with BioRender.com.

1.3 Oral contraceptives

Oral contraceptives, otherwise known as birth control pills, can be prescribed by doctors or medical professionals to treat dysmenorrheic symptoms. There are predominantly two types of them: combined estrogen-progesterone (also known as combined oral contraceptives, COC) and progesterone-only pill (POP) [22]. For the purpose of menstrual pain treatment, COC is most commonly prescribed since estrogen is the hormone that controls the menstrual cycle, and progesterone prevents pregnancy [22].

There are numerous pathways for the oral contraceptives to alleviate menstrual pain. First, the main female sex hormones (estrogen and progesterone) soothe the pain by suppressing ovulation [13]. The suppression of ovulation lessens the contraction of the uterus, which is the physical cause of dysmenorrhea. Second, the main female sex hormones can also reduce the production of PG, specifically $PGF_{2\alpha}$ [22]. Third, consuming oral contraceptives can balance the fluctuating hormone levels [13, 22]. How women perceive pain is different from men; when the main sex hormones—estrogen and progesterone—levels fluctuate, it increases the pain intensity and perception [13]. During menstruation, when the main sex hormone level significantly fluctuates, Athnaiel et al. have reported that there was a “greater prevalence of pain in women, as well as lower pain threshold” [13]. Therefore, providing stable hormone levels by the intake of oral contraceptives serves as a protective mechanism against nociception in females.

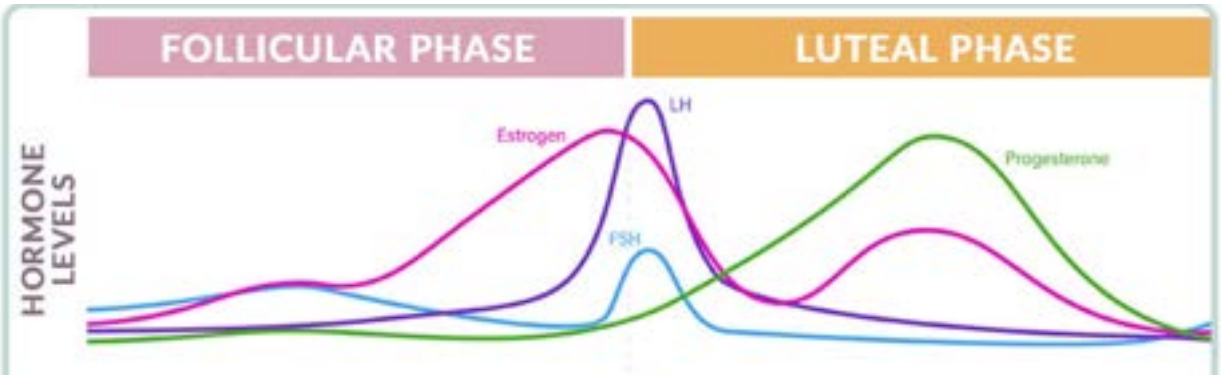

Figure 10. Rise and fall of sexual hormone level [9].

1.3.1 Side effects of oral contraceptives

The following is the list of possible side effects of consuming oral contraceptives [23].

- Abdominal cramping or bloating
- Acne
- Appetite changes
- Back pain
- Breast pain, tenderness, or swelling
- Changed interest in sexual activity
- Darkening skin on the face

- Diarrhea
- Difficulty wearing contact lenses
- Dizziness
- Fatigue
- Gas
- Nausea
- Nervousness
- Rash
- Trouble sleeping
- Vomiting
- Weight changes

While oral contraceptives are widely prescribed to treat dysmenorrhea, it still has a long list of side effects. While all medications do carry side effects to a certain degree, the side effects of oral contraceptives are much more common than other medications. Such common medication to treat common health conditions must seek improvements to reduce the possibility of having side effects.

Pain-Related Condition	Major Biochemical Pathways	Main Findings
Headaches	Estrogen CGRP	Biological females are more likely to experience headaches due to the impact of estrogen on the potent vasodilator, CGRP. This is especially prevalent during pregnancy and in biological females receiving estrogen oral contraceptive pills. Male transgender patients receiving hormone replacement therapy experienced more pain than their female transgender counterparts highlighting the impact of sex hormones on pain perception.
Temporomandibular Disorders	Estrogen Neuropeptide Y Galanin mRNA	Biological females are more likely to experience temporomandibular pain prior to estrogen peak and ovulation. Females receiving steady estrogen replacement through oral contraceptives, were less likely to experience pain. Elevated neuropeptide Y and galanin mRNA are also commonly observed, contributing to the impact of estrogen on pain perception.
Fibromyalgia	VMAT-2 Estrogen	Postmenopausal women are more likely to experience pain related to fibromyalgia. Estrogen replacement reduces the pain by 50%, confirming the benefit of steady estrogen levels as opposed to the cyclical pattern. In-utero exposure to female hormones places transgender men at higher risk of fibromyalgia than transgender women patients despite hormone replacement therapy.
Visceral Pain	Estrogen Androgens Testosterone	Lack of estrogen increased stress-induced pain sensitivity while testosterone administration reduced the pain sensitivity, confirming the protective features of male sex hormones. Female hormone replacement increased pain sensitivity suggesting similar results in transgender women patients.
Musculoskeletal Pain	TRPV1 Testosterone	Increased mechanical sensitivity is seen in biological female rats and male rats that are not producing the appropriate testosterone levels. Pain is up regulated by the presence of TRPV1 receptors. Testosterone replacement reduced the pain in males but did not influence the female rats.
Female Reproductive Organs	Estrogen NMDA TRPA1 TRPV1	Estrogen upregulated the expression of NMDA, TRPA1, and TRPV1, and all of which play a role in increasing pain perception and enhancing molecular signaling of pain. Transgender men and women are at risk for breast pain. In transgender men, the physical binding increases their pain levels while in transgender women, the hormone replacement therapy seems to precipitate the pain most likely due to tissue changes.

Table 2. A list of potential side effects that could arise from hormone fluctuation [13].

1.4 Recent technologies and other methods Alternative and new pain relief therapeutic approaches

1.4.1 Inositol

Inositol is a type of sugar that can be produced from our own body and is also found in foods [24]. The consumption of inositol may balance the fluctuation of certain chemicals in the body and is known to soothe mental pain, such as panic disorder [24]. Inositol can also be helpful for treating secondary dysmenorrhea, especially polycystic ovary syndrome (PCOS)-caused

dysmenorrhea [24]. However, it also improves the maturation of oocytes, which increases the likelihood of pregnancy [24]. Thus, it is not prescribed or recommended for those who do not want to increase the chance of getting pregnant [24].

1.4.2 Lidocaine

Lidocaine is a local anesthetic agent which “prevents pain by blocking the signals at the nerve endings in the skin” [25]. It is an effective pain killer; it is also known to be especially effective for endometriosis-origin dysmenorrhea [25].

1.4.3 Menthol

Menthol is a “chemical naturally found in peppermint” that can mediate anesthetic properties [26]. It can alleviate the pain of muscle cramps. Thus, menthol is effective for primary dysmenorrhea by controlling the uterus contraction [26].

1.4.4 Temperature

Primary dysmenorrhea consists of uterus contraction, which is the tight movement of the organ’s muscles. As a result, it leads to poor circulation of blood flow. By raising the temperature around the abdomen area, aids such as heating pads can aid in promoting better blood flow, increasing circulation and relaxation of the muscles [27]. Heating pads or other forms of temperature-related methods are a non-pharmaceutical way to relieve menstrual pain.

2. Unknowns in the field of menstrual pain research and biology

2.1 Education on the menstrual cycle and origins of dysmenorrhea

While dysmenorrhea is a common abnormal health condition that affects half of the world’s population, the cause and the treatments are not well-known to the public. Recent studies have revealed a few causes of dysmenorrhea, but the public is not well-informed about the science and current state of research. I advocate for education to start in primary and secondary school, where there are already physical/health education systems in place. One of the ways to inform the public is via the physical/health education (PHE) system in primary and secondary educational institutions. Although PHE is a physical activity-oriented course in the majority of the institutions, the course also provides informative sessions on learning the biology of reproductive systems, how to have a healthy diet and more. Although the majority of the courses do explain that women experience menstrual cycles, common diseases associated with the menstrual cycle are not included in the curriculum. These courses often encompass only the broad surface of the menstrual cycle and miss teaching students that dysmenorrhea can occur and do not offer guidance about abnormal menstrual cycles. A research study conducted by the

University of Alberta shows that “comprehensive and accurate sexual education helps students feel more informed”; in order to raise awareness of dysmenorrhea as a separate process of the menstrual cycle and as a disease [28]. There needs to be improvement in the physical health education system.

Furthermore, many people misunderstand what dysmenorrhea is and how it is caused in the first place. The information about dysmenorrhea itself is not fully disclosed to the public. People often regard dysmenorrhea as a natural condition resulting from menstruation, but the menstrual pain could be a signal for a harmful reproductive disease that is being ignored. Of the two types of dysmenorrhea (primary and secondary), secondary dysmenorrhea is caused by reproductive diseases such as endometriosis, PCOS, uterine fibrosis, and more. The exact causes of these diseases are not known. When people are not aware of the exact cause of an abnormal health condition, it may have negative psychological pressure on the individuals that can manifest as people blaming their diet, sexual activities, sleep schedule and more, which may not be well-founded in the biology of dysmenorrhea.

Since the general perception of dysmenorrhea is that it is a natural condition, people often miss out that there might be an irregularity in their health. While most secondary dysmenorrhea causes are not detrimental to people’s lives, each disease may disturb the individual’s well-being and negatively affect their daily lives. Invasive treatments such as surgeries do exist, but leave few options for people experiencing such a chronic disease. The treatment for chronic disease must be actively researched to enhance our awareness of dysmenorrhea as an abnormal health condition and to promote better living standards among biological females.

2.2 Inadequate pain measurements affect dysmenorrhea diagnosis

In many studies measuring the degree of dysmenorrhea, professionals have been relying on a pain perception scale called the visual analogue scale (VAS) (example shown in Figure 11) [29]. The visual representation of the degree of pain using facial expressions may provide an objective increment in pain; however, pain is a subjective measurement and different individuals may perceive the same degree of pain differently.

Normally, the degree of dysmenorrhea is measured by the abdominal pain, but dysmenorrhea also includes back pain, fever, and headache, which are other factors to consider when measuring pain. Thus, the current scientific community lacks an objective measurement of pain. The development of objective measurement will provide a solid evaluation method.

I suggest that pain measurement scales should be improved to objectively quantify diverse types of pain measurements. Furthermore, it should be developed to include all other symptoms that could be related to dysmenorrhea as it not only includes abdominal pain. Such improved measurement could help the patients to understand their pain perception within a given range and it could also provide an objective database for medical professionals to utilize in developing treatments.

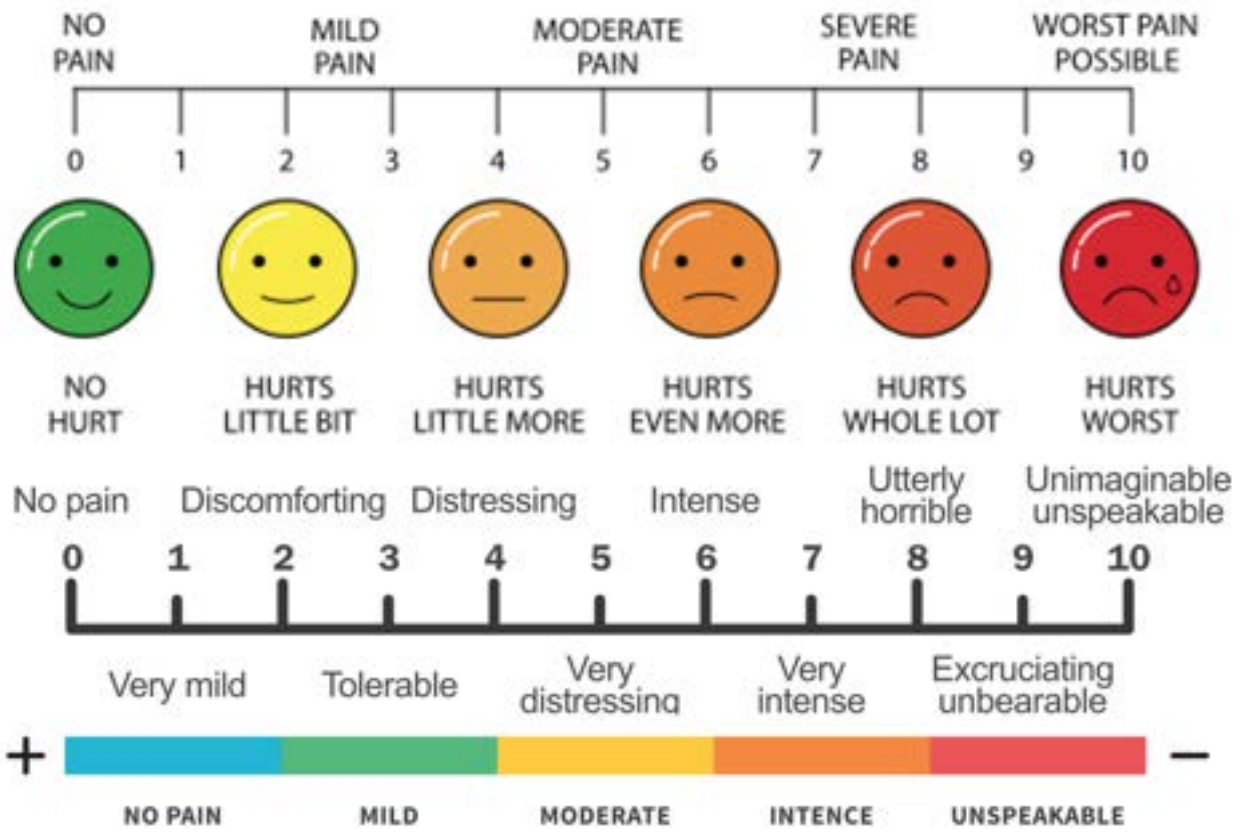

Figure 11. Visual analogue scale (VAS) [30].

As seen in Figure 12, other types of pain measurements are using the Moos Menstrual Disorder Questionnaire (MMDQ) [29]. MMDQ provides more detailed, dysmenorrhea-focused questions to evaluate the patient's symptoms. Although such detailed qualitative observations may provide a more personal and customized narrative of the patient, it is still inadequate when conducting a large data-based experiment which requires quantitative representation.

Menstrual Distress Questionnaire (MEDI-Q)

Cassioli, E., Rossi, E., Melani, G., Faldi, M., Rellini, A. H., Wyatt, R. B., Oreste, C., Vannuccini, S., Petraglia, F., Rivera, V. & Castellini, G.

Instructions - Please carefully review the list of provided symptoms. Please answer question A, for each symptom that you have experienced during your periods in the last 12 months. If you did not experience a particular symptom, please answer "No" and skip to the next symptom on the list. However, if you did experience a symptom, please also answer questions B, C, and D regarding the impact of that symptom on your functioning and quality of life.

A. On average, in the past year on the days you had your period, did you…				**If you had this symptom, to what degree it interfered with your quality of life, your recreational or work activities, or your social relationships…**													
				B. …on days when you were menstruating?				**C. …during the premenstrual phase (in the 7 days before the start of menstruation)?**					**D. …during the other days (outside the menstrual/premenstrual phase)?**				
	Yes, more than half of the times I've had my period	Yes, less than half the times I've had my period	No (Skip to next item)	Not at all	A little	Moderately	Very much	Not at all	A little	Moderately	Very much	Never had this symptom during the premenstrual phase	Not at all	A little	Moderately	Very much	Never had this symptom during the other days
1. …have pain in your lower abdomen?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. …have pain when urinating?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. …have pain during bowel movement?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. …have muscle/bone/joint pain?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5. …feel bloated or did you experience breast tenderness?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
6. …experience nausea?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
7. …have headaches?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8. …have digestive problems (heartburn, uncomfortable sense of fullness after meals …)?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9. …have diarrhea?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10. …have constipation?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
11. …have discomfort due to vaginal bleeding (fear of stains or odors, discomfort from the tampon, difficulty or embarrassment during sexual activities…)?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
12. …have the feeling of being dirty?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
13. …feel excessively sad (easily crying, little drive to do things, loss of interest in usual activities …)?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Figure 12. The Moos Menstrual Disorder Questionnaire (MMDQ) [31].

A Possible technology to measure dysmenorrheic pain involves utilizing a period cramp simulator. The period cramp simulator was initially designed for biological men to experience what menstrual abdominal pain is like. Nevertheless, since the increments for the simulator are quantitative, they may be used to objectively measure the pain.

2.3 The molecular biology of dysmenorrhea pain relief

A better molecular understanding of the currently available treatments for dysmenorrhea would greatly improve how effective they are in pain relief. There are numerous unknown biochemical pathways of pain relief used to treat dysmenorrhea. One molecular component that is known to be related to menstrual pain that this paper has reviewed is the COX enzyme. Some work has suggested that there is COX activity in the uterus, but the exact location and the timing of the COX enzyme's activity is still an active area of research. Acetaminophen, which primarily works around the nervous system and near the cranial parts, is being studied for a possible discovery of a new COX enzyme, COX-3. Because acetaminophen is different from NSAIDs, which work

along the gastrointestinal tract, a number of studies have suggested that there might be a new type of COX enzyme designed for acetaminophen to work in the nervous system. However, much of the information is still not discovered. It would be interesting to know how specific COX-3 enzyme activity is throughout the body and how it is affected by hormone fluctuations.

2.4 How Additional Factors Affect Treatment Efficacy

The efficacies of various ways to deliver pharmaceutical treatments for dysmenorrhea have not been thoroughly investigated. The treatments that were introduced in this paper are mostly prescribed by doctors to be taken via oral consumption. Nonetheless, other forms of consumption such as through the intravenous route (through a vein), intramuscular route (through muscles), subcutaneous route (needle injection), and more might be more effective in specific cases.

For example, intravenous ibuprofen is available for newborn babies or elderly patients who cannot orally consume medication. It is “an attractive option for the treatment of pain in the acute post-operative setting and for use in the critically ill population” [32]. Oral consumption of pharmaceuticals requires the active ingredient to be digested and can access many parts of the body. However, the dilution of the active ingredient may be impossible in certain situations, and the absorption in certain tissues may be ineffective. Directly delivering the pharmaceutical in other ways to the organ of interest may concentrate the active ingredient. Nonetheless, not enough research has been done to determine whether oral consumption is the best route or whether other routes of delivery could be more effective specifically for addressing dysmenorrhea pain.

Aside from the method of pharmaceutical delivery, there are a number of additional factors like genetic history, demographic, psychological factors, and socioeconomic factors that all potentially change the biochemistry of pharmaceuticals in the body. While some efforts in the medical field have been made to include a diverse pool of people in studies broadly, treatments designed for specific individuals are not a reality in our current system and we are far from having a complete picture of how every factor affects pharmaceutical drug efficacy.

The study of dysmenorrhea also lacks an overview of how it may distinctly affect different demographics. Since dysmenorrhea pain can be influenced by psychological factors, muscle contraction, and reproductive disease, the studies should show the differences between certain age groups, socioeconomic status, and nulliparity (“the state of a woman who has never given birth to a potentially viable baby”) [33]. I anticipate that in the future as medicine becomes more personalized, we will learn much more about how other subtle factors affect the efficacy of pharmaceuticals.

3. Future Research Directions

After reviewing the currently available methods to treat dysmenorrhea, I came to the conclusion that improvement should be made in certain aspects.

3.1 Side-effects of NSAIDs and acetaminophen

Although NSAIDs and acetaminophen can be purchased without a professional's prescription, sometimes they cause side effects on the consumer. The side effects are listed down below.

- Indigestion
- Stomach ulcers
- Headaches
- Drowsiness
- Dizziness
- Allergic reactions

Over-the-counter medications are relatively cheaper than oral contraceptives or other types of prescribed medications. Such medications are much more largely available around the world to women in various socio-economic classes who are suffering from dysmenorrhea. Consequently, there needs to be more active research to improve the efficacy of NSAIDs and acetaminophen for pain relief. While eliminating the side effects may be impractical, there could be more research on what triggers such side effects and could build a medical profile of certain types of consumers who should not intake certain types of NSAIDs or acetaminophen.

3.2 Medication targeted solely to treat dysmenorrhea

While many methods are available to treat dysmenorrhea, we still lack a definitive treatment designed for people suffering from dysmenorrhea. NSAIDs and acetaminophen primarily increase the pain threshold of a person and inhibit the production of various PGs; whereas oral contraceptives control hormones (progesterone only or a combination of progesterone and estrogen). The central problem of these medications or other methods is that they are not designed to treat dysmenorrhea only.

Dysmenorrhea disturbs many women's daily lives and there needs to be an improved medication to treat it. Studying the origin of dysmenorrhea and the current medications, I suggest that a medication which could ease the contraction of the uterine muscles could be an alternative method without altering hormone levels or other reproductive biochemical pathways.

4. Impact of Other Areas of Studies (Beyond biochemistry, towards genetics and neuroscience)

4.1 Genetics

A recent study has revealed a correlation between dysmenorrhea and genetic component. According to Jones et al., their analysis has revealed "one-genome wide significant (GWS) association ($P < 5 \times 10^{-8}$) at a region on chromosome 1p13.2" [5]. Also, the study presented their observation of "enrichment for active marks that denote the presence of promoter and enhancer elements specifically in fat and ovary tissues, both of which are highly relevant tissues for the pathophysiology of dysmenorrhea" [5]. Contemporary biological analysis all comes down to genetics; when the genetic components of a specific disease or symptoms are disclosed, then we are one step closer to identifying the cause and eventually inventing a solution. While genetic studies of dysmenorrhea are not yet included in an active field of research, it is certain that genetics and epigenetics will provide significant support in developing treatments for dysmenorrhea.

4.2 Neuroscience

Studying the neurological pathway of pain may also provide a clue for developing treatments for dysmenorrhea. Specifically focusing on the pain perception and electrical transmission between neurons may be a helpful piece of information in creating a method to increase pain threshold. I anticipate that elucidating how the uterus is innervated will help expand our knowledge and improve the efficacy of the current treatments.

Integrating information from other areas of biology and neuroscience will, therefore, guide us through developing improved treatments for dysmenorrhea and enhance our understanding of dysmenorrhea itself as well.

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