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Mechanisms and Management of Dysmenorrhea: Current Understanding and Novel Therapeutic Directions

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Abstract: Dysmenorrhea significantly impacts the quality of life and health of many women worldwide, with primary dysmenorrhea being a major component. Primary dysmenorrhea is primarily driven by the excessive production of prostaglandins, which are responsible for regulating uterine contractions and the shedding of the endometrium. While prostaglandins are essential for normal bodily functions, their overproduction during menstruation leads to severe cramps and considerable pain. In this review, we examine the key biological pathways that contribute to dysmenorrhea, along with the mechanisms behind current treatment strategies and their effectiveness. Based on the current understanding of dysmenorrhea's underlying mechanisms and the insights gained from the reviewing process, we propose potential new drug targets for treatment. Furthermore, we offer comprehensive recommendations for managing dysmenorrhea, combining the results of the further analysis of our previous survey data. We also emphasize the significance of interdisciplinary research, with collaboration across various fields to enhance our understanding and improve the comprehensive management of dysmenorrhea, ultimately benefiting women's health and well-being more effectively.

Keywords: Dysmenorrhea, Novel Therapeutic Targets, Women's Health

1. Introduction

Menstrual health is a crucial aspect of women's well-being [1]. With menstruation occurring over 400 times in a lifetime, it should be a natural process, not marked by constant pain. However, dysmenorrhea affects 45-95% of women globally [2], impacting daily life and mental health [3]. Dysmenorrhea is classified as primary (PD) or secondary (SD). PD refers to menstrual pain without underlying pelvic disease, while SD results from conditions such as endometriosis [4]. PD is primarily linked to excessive prostaglandins (PGs), which trigger strong uterine contractions and pain [5]. Understanding PG mechanisms can improve menstrual health and pain management.

Despite its prevalence, dysmenorrhea treatment remains limited [6]. Broad-spectrum painkillers, like NSAIDs, are the most used treatment, yet they are not specifically designed for dysmenorrhea [7][8][9][10]. While NSAIDs are the best initial therapy, about 18% of patients report minimal or no relief (NSAID-resistant dysmenorrhea) [11]. Additionally, long-term or high-dose use can cause gastrointestinal, cardiovascular, and organ complications [10][12]. These side effects highlight the need for more targeted, safer therapies for dysmenorrhea.

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There has been little progress in developing effective dysmenorrhea treatments [2], reflecting a broader neglect of women's health issues. This research systematically reviews the biological mechanisms behind menstruation and dysmenorrhea, evaluates current treatments, and incorporates first-hand survey data to propose improved management strategies. By increasing public awareness and understanding, we aim to enhance solutions for dysmenorrhea and address unmet women's health needs.

2. What is the menstrual cycle?

The female reproductive system includes the vulva, vagina, uterus, fallopian tubes, and ovaries [13]. The endometrium, lining the uterus, plays a crucial role in the menstrual cycle, a 28-day process preparing the body for pregnancy [13].

The menstrual cycle depends on interactions between the uterus and ovaries. Each month, the ovaries prepare an egg under FSH and LH regulation, while estrogen and progesterone stimulate endometrial thickening for possible implantation [14]. If fertilization does not occur, the egg shrinks and is reabsorbed [14]. As estrogen and progesterone decline, the endometrium sheds, forming menstrual blood [14]. Uterine contractions assist in this process [13].

The endometrium undergoes three phases: proliferative, secretory, and menstrual [14]. Beyond supporting pregnancy, it prevents ectopic implantation, which could be harmful.

3. How PGs affect menstrual pain

Prostaglandins (PGs) regulate uterine contractions necessary for endometrial shedding [15]. However, excessive PG levels contribute to severe menstrual pain [16]. Three primary pathways explain PG-induced dysmenorrhea:

3.1. Pathway 1: Stimulating Uterine Contractions

During menstruation, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and prostaglandin E_2 (PGE_2) are released as the endometrium sheds. At the luteal phase's end, decreased progesterone and estrogen upregulate collagenases, inflammatory cytokines, and MMPs [17]. MMPs break down the endometrium, releasing phospholipids converted into arachidonic acid by uterine phospholipases. Arachidonic acid is processed by COX-1 and COX-2 into PGH2, which serves as a precursor for prostacyclins, PGE_2, $PGF_{2\alpha}$, and thromboxane A_2 (TXA_2) [9].

Each compound has distinct roles: TXA_2 promotes vasoconstriction and platelet aggregation [18]; PGE_2 induces inflammation and vasodilation, attracting immune cells [19]; $PGF_{2\alpha}$ causes uterine constriction and pain [20]; and prostacyclin promotes vasodilation and inhibits platelet aggregation [19]. $PGF_{2\alpha}$ and PGE_2 elevate uterine tone and induce hypercontractility, overstimulating muscles and causing pain [21].

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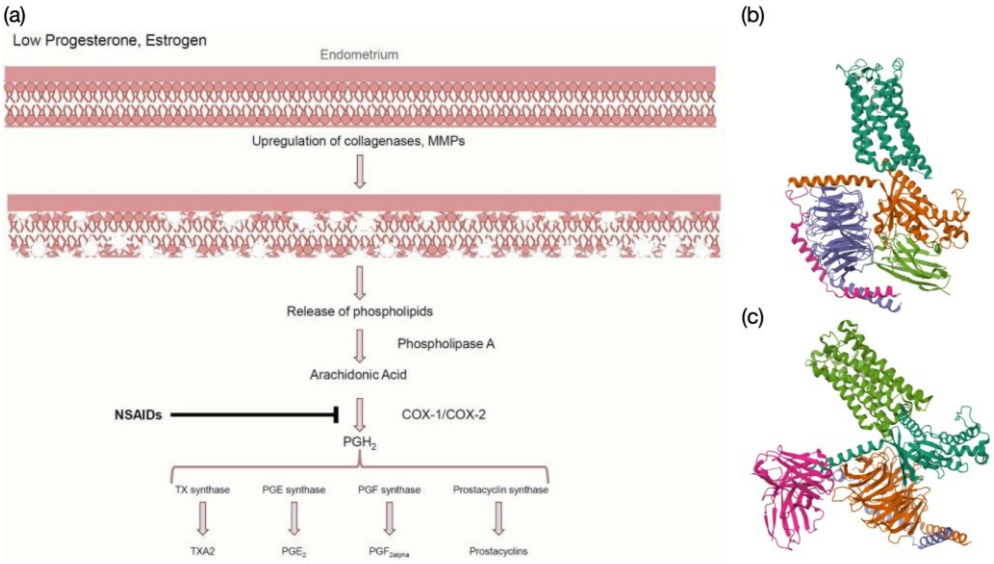

Figure 1: NSAID pathway and prostaglandin receptor structures.

(a) NSAID Pathway: Low progesterone and estrogen levels trigger phospholipid release, leading to arachidonic acid synthesis. COX-1/COX-2 enzymes convert arachidonic acid into PGH_2, a precursor for various prostaglandins. NSAIDs inhibit COX enzymes, reducing prostaglandin synthesis and alleviating pain [9]. (b) PGE_2-EP_2 Receptor Complex: Cryo-EM structure of the PGE_2-bound EP_2-Gs complex (PDB: 7CX2), a GPCR mediating vasodilation and inflammation [22]. (c) $PGF_{2\alpha}$ -FP Receptor Complex: Cryo-EM structure of the $PGF_{2\alpha}$ -bound FP-Gq complex (PDB: 8XJL), a GPCR involved in smooth muscle contraction and uterine function [20].

3.2. Pathway 2: Reducing Uterine Blood Flow (Ischemia)

Prostaglandins induce vasoconstriction, narrowing blood vessels and causing ischemia in uterine muscles, reducing oxygen supply and leading to dysmenorrhea pain [23]. Since stronger muscle contractions require more oxygen, ischemia worsens fatigue and pain [23].

3.3. Pathway 3: Sensitizing Nerve Endings

Prostaglandins, especially $PGF_{2\alpha}$, heighten uterine nociceptor sensitivity by lowering the pain perception threshold, amplifying discomfort during contractions, even when contractions are not excessively strong [2].

4. Current Common Ways to Manage Menstrual Pain

Primary dysmenorrhea is managed through nonpharmacologic and pharmacologic methods.

Heat therapy is a preferred option with no side effects [24]. Studies comparing it to ibuprofen and acetaminophen confirm its effectiveness in pain relief [25]. However, for severe symptoms, heat therapy alone may not be sufficient [25]. Exercise and a balanced diet are also recommended, as evidence supports their role in reducing pain intensity [26][27]. Dietary adjustments, such as fish oil and vitamin B1 supplements, can help alleviate symptoms. Omega-3 fatty acids in fish oil inhibit prostaglandin synthesis, reducing pain [27]. Vitamin B1 influences nervous system activity and muscle contraction, improving pain perception and reducing uterine contractions [28]. However, while beneficial for long-term health, exercise and diet provide limited immediate relief.

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The most common pharmacologic treatments for dysmenorrhea are NSAIDs and hormonal contraceptives. NSAIDs are the primary choice and have demonstrated effectiveness in placebo-controlled trials [9]. They reduce menstrual pain by inhibiting COX, thereby lowering PGH_2 production from arachidonic acid [9]. Despite this, NSAIDs have several limitations:

1. **Limited Effectiveness**: About 20% of women report no relief from NSAIDs, as seen in a review of 51 clinical trials [9].
2. **Partial Pain Relief**: Many women find NSAIDs insufficient, alleviating some symptoms but not eliminating discomfort [9]. Additionally, the tendency to remain silent about menstrual pain complicates treatment outcomes [29].
3. **Side Effects**: As broad-spectrum drugs, NSAIDs can cause gastrointestinal, cardiovascular, liver, kidney, brain, and lung complications [10]. Developing dysmenorrhea-specific treatments may help minimize these risks.
4. **Impact on Endometrial Shedding**: NSAIDs reduce prostaglandin levels and uterine contractions, potentially affecting proper endometrial shedding [15].

Besides NSAIDs, hormonal contraceptives are another option for menstrual pain relief. However, they have significant side effects, including mood swings, depression, nausea, weight gain, and increased risk of blood clots [30]. Women with a family history or diagnosis of hormone-sensitive cancers are generally advised against using hormonal contraceptives due to their effects on estrogen levels and associated cancer risks [31].

While NSAIDs and hormonal contraceptives are widely used, their limitations highlight the need for more targeted and safer treatment options for dysmenorrhea.

5. New Drug Targets

Although NSAIDs provide relief, they remain ineffective for many patients [10][12]. More targeted therapeutic strategies are needed to better address dysmenorrhea. PGE_2 and $PGF_{2\alpha}$ are the prostaglandins most directly linked to dysmenorrhea [5]. Instead of inhibiting their upstream precursor PGH_2, as NSAIDs do, directly blocking PGE_2 and $PGF_{2\alpha}$ may offer a more effective solution.

We propose two drug design approaches:

1. **Low-Affinity Competitive Antagonists:** Designing antagonists to compete with PGE_2 and $PGF_{2\alpha}$ for their receptors could regulate their activity without completely blocking them [9]. Because these prostaglandins are essential for endometrial shedding and immune functions, antagonists should have low binding affinity to prevent excessive receptor occupation. Slight structural modifications in antagonists may allow partial receptor binding, reducing their activity while maintaining necessary physiological functions (Figure 1, Panel b & c).
2. **Selective Inhibition of PGE_2 and $PGF_{2\alpha}$ Production:** Unlike NSAIDs, which broadly inhibit COX and reduce PGH_2 synthesis, selectively targeting the synthesis of PGE_2 and $PGF_{2\alpha}$ may provide greater efficacy [9]. While this strategy could enhance dysmenorrhea treatment, it may also disrupt other prostaglandin-dependent physiological processes, requiring careful regulation.

Focusing on PGE_2 and $PGF_{2\alpha}$ could offer advantages over NSAIDs, especially for patients unresponsive to traditional treatments [11]. NSAIDs inhibit PGH_2 but do not always proportionally reduce PGE_2 and $PGF_{2\alpha}$, potentially leading to inadequate pain relief. A more targeted approach could improve efficacy while minimizing side effects associated with broad-spectrum NSAIDs [10].

In addition to pharmacologic innovations, we advocate integrating lifestyle modifications. Arachidonic acid, a precursor to PGs, is derived from dietary sources and stored in cell membranes [32]. Reducing dietary intake of arachidonic acid-rich foods may lower PG production. Exercise can

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also modulate PG synthesis by increasing progesterone levels during the luteal phase, reducing phospholipid release from cell membranes [26]. Improved blood circulation from regular exercise ensures adequate uterine blood supply, mitigating muscle contractions induced by ischemia and hypoxia [26].

While lifestyle adjustments may not provide immediate relief, they contribute to long-term symptom reduction, improving overall menstrual health. Further analysis of previous survey data supports a correlation between exercise and reduced menstrual pain severity (Figure 2) [24].

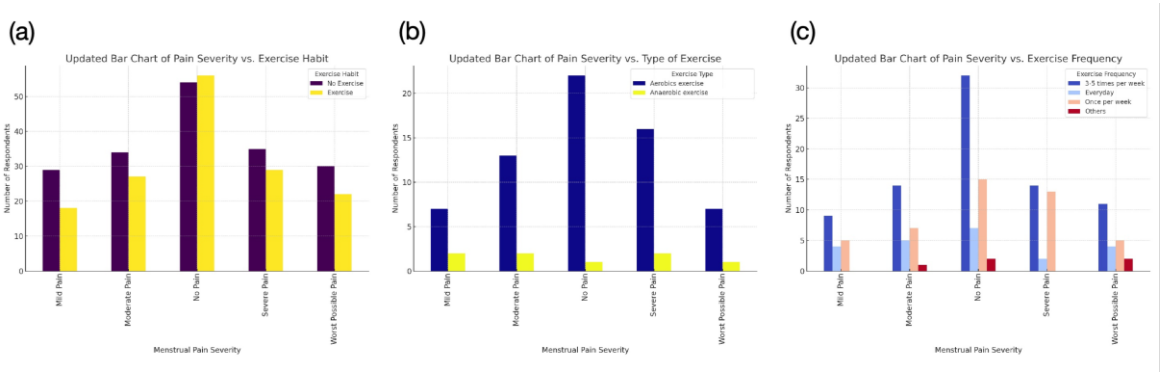

Figure 2: Correlation Between Menstrual Pain Severity and Exercise.

(a) Exercise Habit vs. Pain Severity**:** Individuals who exercise regularly report less severe pain, while severe pain groups have more non-exercisers, indicating a possible link between inactivity and higher pain severity. (b) Exercise Type vs. Pain Severity**:** Aerobic exercise is most common across all pain levels, with the "No Pain" group having the highest aerobic participation. Anaerobic exercise is less frequent and shows no strong correlation with pain levels. (c) Exercise Frequency vs. Pain Severity: Moderate, consistent exercise (3-5 times per week) is most common in the "No Pain" group, suggesting an association between regular exercise and better pain management.

6. Discussion

Dysmenorrhea affects a vast number of women, yet menstrual health remains underprioritized [24]. Research on menstruation is inadequate, and effective dysmenorrhea treatments are still limited.

During this study, I observed significant gaps in menstrual research. For example, there is no standardized definition for menstrual phases; different studies classify them inconsistently, sometimes into three phases and sometimes four, often without clear sources. While the menstrual cycle involves changes in both ovarian and endometrial phases, inconsistent terminology may mislead researchers and hinder progress. This reflects a broader issue: menstrual research lacks a structured framework, emphasizing the need for greater awareness and investment in this field.

This paper has two key objectives. First, to propose a new pharmacological target for dysmenorrhea treatment. While promising, this approach is not the only possibility, as alternative mechanisms need further exploration. Additionally, potential side effects must be addressed. Second, by introducing a new drug target, we hope to stimulate further discussions on menstrual health. Current dysmenorrhea treatments remain inadequate despite the strong demand for pain relief. Many women endure years of menstrual pain without sufficient options. Further analysis of my survey data shows that women, particularly those with severe pain, actively seek better treatments and are willing to try new solutions (Figure 3) [24]. We hope this paper encourages further research and broader therapeutic development. Given that this issue affects approximately 70% of women monthly, it deserves urgent attention [33].

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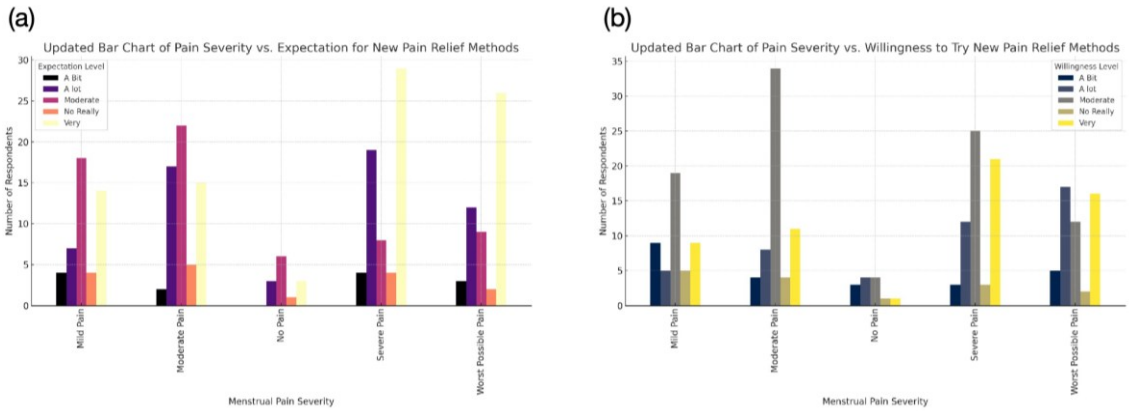

Figure 3: Correlation Between Menstrual Pain Severity and Attitudes Toward New Pain Relief Methods.

(a) Expectation for New Treatments: Individuals with severe pain show the highest expectation for new pain relief methods, while those with little to no pain exhibit lower demand. (b) Willingness to Try New Methods: Those experiencing severe pain are most open to trying new treatments, whereas individuals with little or no pain show the least interest. Each color represents a different expectation level, ranging from "No Really" (low expectation) to "Very" (high expectation).

Moreover, we urge women to advocate for better health solutions rather than silently endure pain. Dysmenorrhea's persistence is not a personal failing but rather a shortfall of existing treatment options. By speaking up, women can raise awareness and drive advancements in healthcare and research.

Addressing menstrual pain also requires an interdisciplinary approach. Pain is influenced by multiple factors [2][4][6]. While this paper explores biological treatments, integrating perspectives from neuroscience, psychology, biomedical engineering, and sociology can enhance understanding and solutions. A multidisciplinary approach will be crucial in advancing dysmenorrhea research and improving women's health outcomes.

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