Nonsteroidal antiinflammatory drug resistance in dysmenorrhea: epidemiology, causes, and treatment

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Although nonsteroidal antiinflammatory drugs can alleviate menstrual pain, about 18% of women with dysmenorrhea are unresponsive, leaving them and their physicians to pursue less well-studied strategies. The goal of this review is to provide a background for treating menstrual pain when first-line options fail. Research on menstrual pain and failure of similar drugs in the antiplatelet category suggested potential mechanisms underlying nonsteroidal antiinflammatory drug resistance. Based on these mechanisms, alternative options may be helpful for refractory cases. This review also identifies key pathways in need of further study to optimize menstrual pain treatment.

Key words: adenomyosis, endometriosis, menstrual pain, nonsteroidal antiinflammatory drugs, oral contraception, primary dysmenorrhea, secondary dysmenorrhea

Introduction

The scope of the clinical problem of menstrual pain was effectively communicated by former First Lady Michelle Obama, when she tweeted, "Why are girls still missing so many days of school because of their menstrual cycles?"[1] Too many women hide this personal stigma, and experience a physical and psychological burden of frequent, severely painful cramps occurring over several days every month, persisting for decades. The transcultural impact of this problem was highlighted when Chinese Olympic medalist Fu Yuanhui acknowledged that menstrual pain affected her Olympic swimming performance.[2] The etiology of menstrual pain remains inadequately characterized,[3] and this limited scientific understanding hinders adequate treatment for women who are unresponsive to first-line options including nonsteroidal antiinflammatory drug (NSAID) therapy. To optimize the management of menstrual pain, further studies of its pathophysiology are needed. This review summarizes current scientific knowledge and associated critical gaps in menstrual pain unresponsive to NSAIDs (Figure 1).

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Received May 29, 2017; revised Aug. 14, 2017; accepted Aug. 31, 2017.

supported by *Eunice Kennedy Shriver* National Institute of Child Health and Human Development HD081709, National Institute of Diabetes and Digestive and Kidney Diseases DK100368, and NorthShore University HealthSystem.

F.F.T. was a consultant for AbbVie Pharmaceuticals. The remaining authors report no conflict of interest.

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0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2017.08.108

Epidemiology of NSAID-resistant dysmenorrhea

Menstrual pain, also known as dysmenorrhea, is common and affects nearly half of reproductive-age girls and women.[4-6] Before the advent of NSAID therapy, it was observed that 10% of high school girls in Los Angeles missed classes because of dysmenorrhea.[7] The development of NSAIDs in 1969 heralded a new era of pain management, and over-the-counter availability of this medication class in 1983 held the promise of resolving dysmenorrhea for many women. Indeed, for most women, NSAIDs are effective for treating dysmenorrhea as demonstrated by a meta-analysis of 35 randomized controlled trials.[8] However, dysmenorrhea still causes 10-20% of US female high school students to miss class during their menses.[9,10] This phenomenon is also seen internationally,[11] with menstrual pain-induced absenteeism occurring at similar or greater rates.[12-14] Further, a review of 51 different clinical trials found that 18% of women report minimal or no relief of menstrual pain with NSAIDs.[15] This failure to relieve pain suggests multiple pathological mechanisms may contribute to treatment unresponsiveness. Clarifying these mechanisms is an obvious critical need in gynecological research.

What causes menstrual pain?

Preclinical research studies suggest prostaglandin (PG)-dependent mechanisms drive dysmenorrhea in a majority of women (reviewed by Maia et al[16] in 2005). The start of menstruation is marked by the simultaneous decrease in circulating progesterone and estradiol, initiating increased transcription of endometrial collagenases, matrix metalloproteinases (MMPs), and inflammatory cytokines (Figure 2). Up-regulated MMPs specifically target and break down endometrial tissue, freeing phospholipids from the cellular membrane. Uterine phospholipases convert available phospholipids to arachidonic acid, which is then synthesized into PG, prostacyclins, and thromboxane-2a via cyclooxygenase (COX)-1 and COX-2. Notably, COX-2 expression is highest during menses.[16] Although 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 effluent in dysmenorrheic

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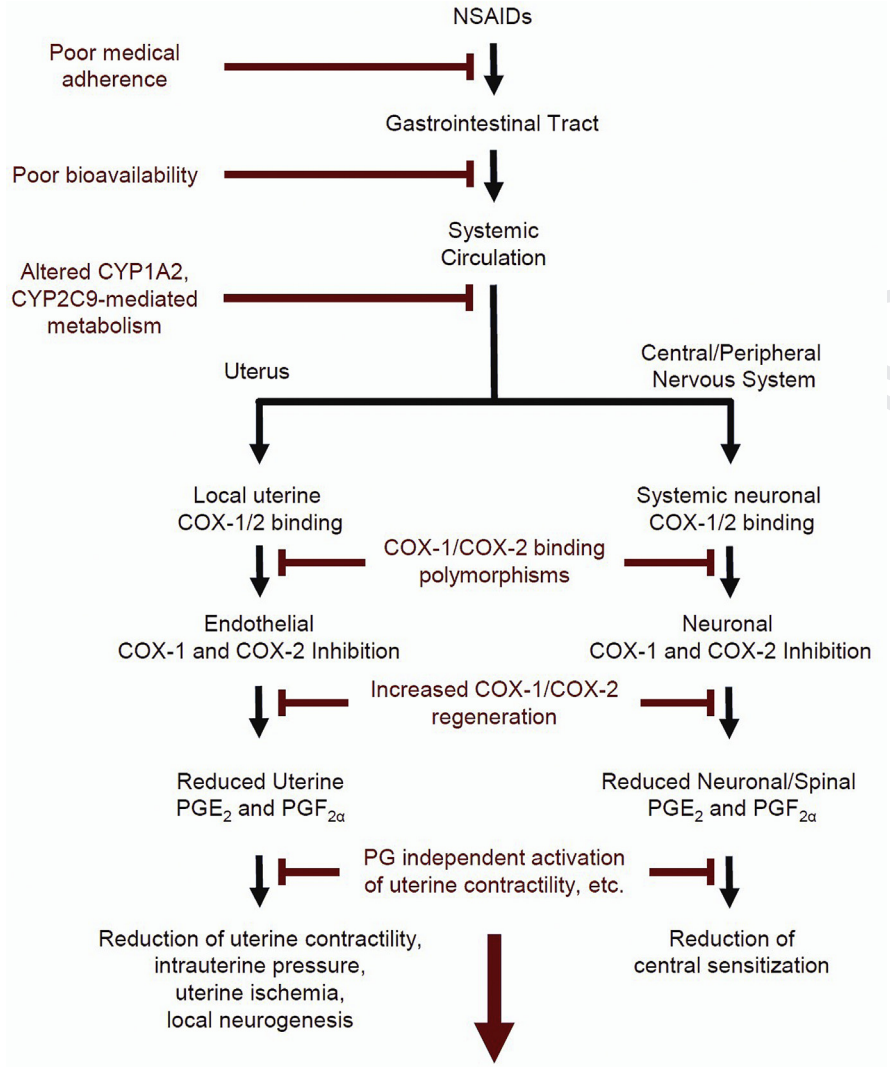
FIGURE 1



Proposed pathway examining nonsteroidal antiinflammatory drug (NSAID)-resistant dysmenorrhea. Many complex mechanisms contribute to development of NSAID-resistant dysmenorrhea. NSAIDs normally reduce menstrual pain via suppression of peripheral and systemic prostaglandins (PG) and corresponding downstream effects (shown in black). Elements on left branch highlight uterine mechanisms while right branch highlights central and peripheral neural mechanisms. Various physiological factors, ranging from poor medical adherence to involvement of PG-independent cascades, may disrupt NSAID efficacy to ameliorate menstrual pain and promote NSAID resistance (shown in red).

COX, cyclooxygenase; *CYP*, cytochrome P450.

Oladosu. NSAID-resistant dysmenorrhea. Am J Obstet Gynecol 2017.

women when compared to healthy controls.[17,18]

The identification of elevated PGE_2 and $PGF_{2\alpha}$ in dysmenorrhea supported the strategy of inhibiting COX-2 with NSAIDs to treat menstrual pain. Nonspecific NSAIDs (Table) bind to both COX-1 and COX-2 to inhibit PG synthesis. More selective NSAIDs known as COX-2 inhibitors alleviate menstrual pain by specifically inhibiting COX-2 activity. Unlike COX-1, which is constitutively expressed, COX-2 is upregulated by stimuli associated with inflammation[19] and during progesterone withdrawal,[20,21] thus making COX-2 inhibitors an appropriate alternative to nonspecific NSAIDs.

Although it is possible that PGs could excite nociceptors and cause pain, it is believed that PGs indirectly cause cramping pain by stimulating uterine contractility.[22] Preclinically, we recently confirmed that $PGF_{2\alpha}$ administration increases uterine contractility and elicits visceral pain.[23] Conversely, drugs that inhibit PG synthesis, such as ibuprofen[24] and naproxen,[25] reduce uterine contractility in dysmenorrheic women. These findings suggest that PGs increase uterine contractility and produce cramping pain via temporary elevations in uterine pressure.[22] Since not all women with dysmenorrhea have alterations in uterine pressure,[26] other mechanisms might contribute to menstrual pain. For example, impaired uterine perfusion was observed in dysmenorrhea[27]; ischemia may also cause cramping pain. In our mouse model of dysmenorrhea, impaired uterine perfusion and hypoxemia also occurred.[23] Although these studies collectively suggest physiological mechanisms underlying dysmenorrhea, they fail to clarify why some women do not respond to NSAIDs.

Anatomical factors

A subset of women with dysmenorrhea, particularly those with delayed presentation after menarche, may harbor separate contributing anatomical factors such as endometriosis, leiomyoma, or adenomyosis; these cases 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.[28] The molecular contributions of anatomical factors to secondary dysmenorrhea are limited. Immunohistological studies investigating endometriosis demonstrated that lesions have increased

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