



THE ROLE OF PROSTAGLANDINS IN PRIMARY DYSMENORRHEA AND THE EFFECTIVENESS OF ANTI-INFLAMMATORY THERAPY

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Abstract

Primary dysmenorrhea is a recurrent menstrual pain syndrome occurring in the absence of identifiable pelvic pathology. Its most accepted pathophysiological model centers on increased endometrial production of prostaglandin F2 α and prostaglandin E2 during menstruation. These mediators intensify uterine contractions, increase intrauterine pressure, reduce uterine blood flow, induce ischemia, and sensitize pain pathways. This article reviews the biological role of prostaglandins, the clinical rationale for NSAID therapy, timing and safety considerations, real-world effectiveness, pharmacovigilance, artificial intelligence, and personalized treatment strategies.

The evidence synthesis shows that anti-inflammatory therapy is pathogenetically justified when primary dysmenorrhea is prostaglandin-dominant. However, treatment success depends on early initiation, correct dosing, patient education, safety screening, and reassessment when response is inadequate. Real-world data and AI-based analytics may help identify patients with poor response, detect adverse drug reaction signals, and improve clinical decision support. The article also discusses how Uzbekistan's developing e-prescription and digital health systems may support safer NSAID use and national evidence generation.

A central conclusion is that NSAID therapy should not be evaluated only as a drug effect, but as a complete clinical strategy that includes diagnosis, timing, adherence, contraindication screening, follow-up, and referral criteria. When this strategy is implemented correctly, prostaglandin inhibition remains a rational first-line approach. When it fails, clinicians should consider secondary dysmenorrhea, central sensitization, inadequate exposure, or non-prostaglandin mechanisms rather than repeating empirical analgesic escalation.

Keywords: primary dysmenorrhea, prostaglandins, PGF2 α , PGE2, cyclooxygenase, NSAIDs, anti-inflammatory therapy, real-world evidence, pharmacovigilance, artificial intelligence, precision medicine.

Introduction

Primary dysmenorrhea represents one of the clearest examples of a clinical symptom in which molecular pathophysiology directly informs treatment. The pain typically begins shortly before or at the onset of menses, peaks during the first one or two days, and occurs without identifiable pelvic pathology. The key biological event is increased prostaglandin production during endometrial shedding.



Prostaglandins transform physiological uterine contractions into painful hypercontractility. PGF2 α increases uterine tone and vasoconstriction, while PGE2 contributes to inflammatory signaling and pain sensitization. The resulting ischemia and activation of nociceptive pathways explain why cyclooxygenase inhibition is effective in many patients.

Nevertheless, anti-inflammatory therapy is often used incorrectly in real life. Many patients take NSAIDs only after pain becomes severe, use subtherapeutic doses, combine analgesics unsafely, or stop treatment because of gastrointestinal symptoms. Real-world evidence is therefore needed to understand effectiveness and safety beyond controlled trials.

Materials and Methods

This article was prepared as an analytical narrative review with elements of a scoping review. Evidence was searched and synthesized from PubMed, Scopus, Web of Science, Embase, Cochrane Library, WHO, FDA, EMA, ESHRE, and methodological literature on real-world evidence and artificial intelligence in health care. The search strategy combined terms related to dysmenorrhea, primary dysmenorrhea, prostaglandins, NSAIDs, menstrual pain, endometriosis, real-world data, pharmacovigilance, machine learning, natural language processing, and clinical decision support.

The inclusion criteria covered clinical guidelines, systematic reviews, meta-analyses, randomized controlled trials, pharmacoepidemiological studies, regulatory documents, and high-quality narrative reviews relevant to dysmenorrhea, menstrual health, prostaglandin biology, anti-inflammatory therapy, real-world evidence, and AI-based clinical analytics. Publications with unclear methodology, unsupported claims, purely promotional content, or duplicated data were excluded from the core synthesis.

The methodological framework distinguished efficacy from effectiveness. Efficacy was interpreted as benefit under controlled conditions, mostly from randomized trials, whereas effectiveness was interpreted as benefit in routine care, where treatment timing, adherence, self-medication, comorbidity, access to care, and patient education modify outcomes. For observational evidence, the review discusses Propensity Score Matching, Inverse Probability Weighting, Cox regression, Kaplan-Meier analysis, target trial emulation, causal inference, survival analysis, machine learning, deep learning, natural language processing, and large language models.

Analytical framework for RWD, RWE and AI methods

Real-world data were interpreted as routinely collected health data generated outside the narrow architecture of a randomized trial. In the context of dysmenorrhea, this includes electronic health records, outpatient records, emergency visits, e-prescriptions, pharmacy dispensing data, imaging reports, laboratory information systems, school or workplace absence records when ethically available, pharmacovigilance reports, menstrual tracking applications, and wearable-derived physiological measures. Real-world evidence was defined as clinically interpretable evidence produced from RWD through transparent epidemiological, statistical, and computational methods.

The review treats RCTs and RWE as complementary rather than competing forms of evidence. RCTs protect internal validity through randomization, protocolized therapy, and close follow-up; however, they often underrepresent adolescents, patients using over-the-counter analgesics, women with irregular access to care, and those whose treatment behavior is shaped by stigma or cost. RWE



can address these implementation questions, but it requires active control of confounding, missingness, misclassification, immortal time bias, and selection bias.

Propensity score matching can create more comparable treatment groups by matching patients with similar baseline probability of receiving a given therapy. Inverse probability weighting uses the propensity score to weight observations and estimate an average treatment effect in a pseudo-population. Cox regression and Kaplan-Meier curves are useful when the outcome is time-dependent, such as time to reconsultation, time to therapy switching, or time to suspected endometriosis referral. Target trial emulation strengthens observational studies by forcing investigators to specify eligibility, treatment strategies, assignment time, follow-up, outcome, and estimand before analyzing routine data.

Causal inference was considered essential because observational associations can easily be misread as treatment effects. For example, women receiving stronger analgesics may appear to have worse outcomes not because the drugs are harmful, but because baseline pain severity is higher. Machine learning, deep learning, natural language processing, reinforcement learning, and large language models were evaluated as tools for prediction, classification, signal detection, and evidence synthesis. They were not treated as substitutes for clinical judgment, biological plausibility, or regulatory oversight.

Results

Prostaglandin pathway and uterine ischemia

Progesterone withdrawal at the end of the luteal phase destabilizes the endometrium and promotes release of phospholipids. Arachidonic acid is converted through cyclooxygenase pathways into prostaglandins and thromboxanes. Increased PGF2 α and PGE2 concentrations are associated with stronger uterine contractions, higher resting uterine pressure, vasoconstriction, tissue hypoxia, and cramp-like pain.

The intensity of symptoms varies because prostaglandin biology interacts with vasopressin, leukotrienes, inflammatory cytokines, oxidative stress, pain sensitivity, sleep, psychological stress, and social context. A poor response to NSAIDs should therefore prompt reassessment for timing, adherence, secondary dysmenorrhea, and central sensitization.

Pathogenesis of menstrual pain



Figure 1. Prostaglandin-centered pathogenesis of primary dysmenorrhea.

Effectiveness of NSAIDs

NSAIDs reduce menstrual pain by inhibiting COX-mediated prostaglandin synthesis. Their clinical effectiveness is strongest when therapy is started early, before maximal prostaglandin release has produced severe uterine hypercontractility. Ibuprofen, naproxen, mefenamic acid, and related agents are commonly used, but choice should be individualized according to safety profile and patient characteristics.

The phrase “NSAID failure” should be used carefully. Failure may reflect delayed administration, insufficient dose, irregular intake, vomiting, severe prostaglandin surge, or non-prostaglandin pain mechanisms. A structured trial over several cycles, with a pain diary and clear instructions, provides more reliable evidence than a single unsupervised dose.

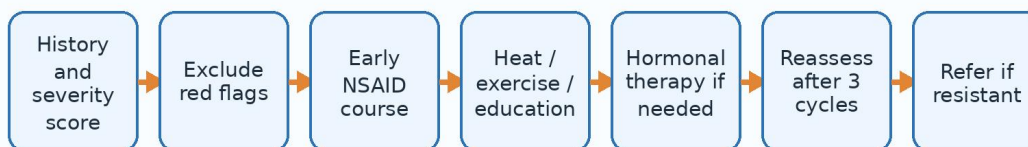
Evidence-based management pathway

Figure 2. Practical management pathway for dysmenorrhea.

Safety and pharmacovigilance

NSAID safety assessment is essential even when the drug is used for only a few days per month. Gastrointestinal ulcer risk, renal disease, dehydration, anticoagulants, corticosteroids, aspirin-sensitive asthma, cardiovascular risk, and possible pregnancy should be considered. Pharmacovigilance systems should capture adverse reactions related to menstrual pain treatment, including over-the-counter self-medication.

Drug safety signal detection can identify patterns that are invisible in individual encounters. If a specific NSAID is repeatedly associated with gastrointestinal complaints in young women, or if high-dose self-medication is common, pharmacovigilance analytics can inform safer prescribing, pharmacist counseling, and public education.

RWE, AI and precision medicine

RWD sources such as EHRs, e-prescriptions, mobile diaries, registries, claims data, and pharmacovigilance reports can evaluate whether NSAID therapy works in routine care. Propensity score matching, IPW, Cox regression, Kaplan-Meier analysis, target trial emulation, and causal inference can reduce bias when comparing treatment strategies.

Machine learning may predict response to NSAIDs by combining cycle characteristics, pain severity, timing of drug intake, comorbid symptoms, sleep, stress, and previous treatment response. NLP can extract clinically meaningful menstrual pain narratives from free-text notes. Large language models may assist with evidence synthesis, but clinical recommendations must remain expert-supervised and source-verified.

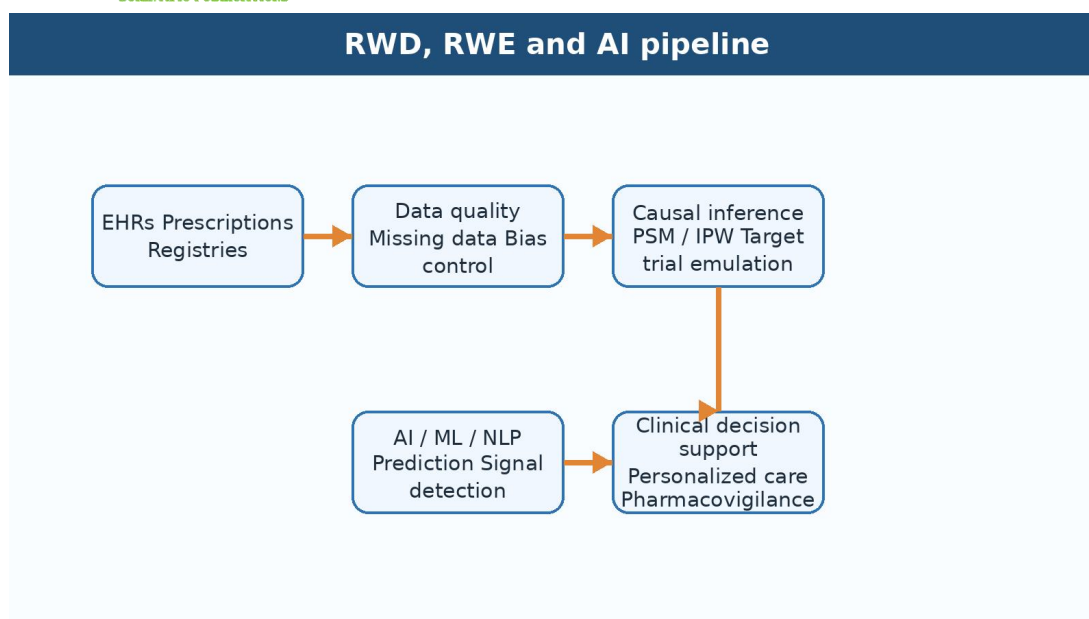


Figure 3. Real-world evidence and artificial intelligence pipeline for menstrual pain research.

Table 1. Mechanistic rationale for anti-inflammatory therapy

Mechanism	Clinical consequence	Therapeutic implication
COX activation	PGF2 α and PGE2 increase	Early NSAID initiation
Uterine hypercontractility	Cramping pain	Planned short course
Vasoconstriction	Ischemic pain	Avoid delayed rescue-only use
GI risk	NSAID adverse effects	Individual safety assessment

Table 2. Real-world outcomes for NSAID effectiveness studies

Outcome	Meaning	Data source
Pain reduction	Patient-reported benefit	Mobile diary, EHR
Therapy switching	Insufficient control	E-prescription
Reconsultation	Persistent symptoms	EHR, claims
Adverse reaction	Safety signal	Pharmacovigilance

Biological interpretation of prostaglandin dominance

The prostaglandin hypothesis is clinically powerful because it links a predictable endocrine event with a measurable inflammatory cascade and a modifiable therapeutic target. Luteal progesterone withdrawal initiates endometrial breakdown, phospholipase activity, arachidonic acid release, and cyclooxygenase-mediated prostanoid synthesis. When prostaglandin production is excessive, uterine contractions become more frequent, less coordinated, and more painful. High intrauterine pressure reduces perfusion, creating ischemic pain and systemic symptoms.

The model also explains the timing of symptoms. Pain is most intense near the beginning of menstrual bleeding, when prostaglandin release from the shedding endometrium is greatest. This is why early NSAID administration has a stronger mechanistic rationale than late rescue use. If a patient waits until severe pain is established, prostaglandin-mediated hypercontractility and nociceptive activation may already be advanced, and analgesic response can appear weaker.



At the same time, prostaglandin dominance is not synonymous with prostaglandin exclusivity. Vasopressin may increase uterine activity; leukotrienes may contribute when NSAID response is incomplete; inflammatory cytokines may affect pain sensitivity; and repeated severe pain may promote central sensitization. This biological complexity justifies a stepped but flexible treatment plan rather than a one-drug model.

Clinical determinants of NSAID effectiveness

The effectiveness of anti-inflammatory therapy depends on five practical variables: correct diagnosis, early timing, adequate dose, regular short-course administration, and safety-compatible patient selection. A patient with primary dysmenorrhea who starts ibuprofen or naproxen at the onset of symptoms and continues as directed for the first painful days is biologically different from a patient who takes a single low dose after vomiting, missed school, and several hours of severe pain.

Clinical counseling should therefore be treated as part of the intervention. Patients need to understand that the purpose of NSAID therapy is not only to suppress pain perception but to reduce prostaglandin synthesis before maximal uterine hypercontractility develops. A menstrual pain diary can document cycle day, pain score, drug timing, dose, adverse symptoms, and functional outcome. This converts an informal self-medication pattern into a measurable therapeutic trial.

Several findings suggest that a diagnosis of primary dysmenorrhea should be reconsidered: progressive worsening, pain beginning well before menstruation, persistent pelvic pain after bleeding stops, dyspareunia, dyschezia, urinary pain, abnormal bleeding, infertility, fever, pelvic mass, or failure of correctly used NSAID therapy over several cycles. In these cases, escalation should mean diagnostic reassessment rather than simply increasing analgesic exposure.

RWD outcomes for anti-inflammatory therapy

Routine data can evaluate outcomes that trials often measure incompletely. Pain reduction is important, but real-world effectiveness also includes school attendance, work productivity, emergency visits, repeated consultations, therapy switching, patient satisfaction, adverse reactions, and persistence of treatment benefit over multiple cycles. E-prescription data can show whether a patient receives repeated NSAID prescriptions without diagnostic escalation, which may indicate undertreated secondary dysmenorrhea.

Mobile applications can capture the temporal relationship between bleeding, pain, drug intake, and symptom relief. If combined with clinical records, they may help distinguish poor adherence from pharmacological non-response. For example, a patient who reports good relief when NSAIDs are taken early but poor relief when intake is delayed does not need a new diagnosis; she needs a better timing strategy. Conversely, persistent severe pain despite correct timing and dose suggests the need for further evaluation.

AI-supported pharmacovigilance and stewardship

Pharmacovigilance in primary dysmenorrhea should focus on the safety of repeated intermittent NSAID exposure. AI can assist by clustering adverse event narratives, identifying duplicate reports, detecting temporal associations, and highlighting unusual patterns by age, dose, comorbidity, or co-medication. NLP may extract mentions of over-the-counter analgesic combinations from clinical notes, which are often missing from structured medication lists.



AI-supported stewardship can also identify potentially unsafe patterns: frequent high-dose NSAID use, overlapping NSAIDs, NSAID use in patients with renal risk, repeated prescriptions without reassessment, or symptoms suggesting gastrointestinal injury. Such tools should be designed as clinical decision support, not as autonomous prescribers. Alert fatigue is a real risk; recommendations must be specific, explainable, and clinically actionable.

Precision medicine perspective

A precision approach to primary dysmenorrhea begins with stratifying patients by phenotype. A patient with isolated cramping pain and rapid response to early NSAIDs differs from a patient with severe systemic symptoms, migraine, heavy bleeding, gastrointestinal intolerance, or suspected endometriosis. Treatment can then be adapted: NSAID optimization, alternative NSAID selection, hormonal suppression, non-pharmacological support, or referral.

Future pharmacogenetic work may clarify whether variants affecting NSAID metabolism, prostaglandin pathways, pain sensitivity, or inflammatory signaling predict benefit or harm. For now, the strongest personalized tools remain history, safety screening, response tracking, and shared decision-making. Precision medicine should reduce unnecessary exposure and diagnostic delay, not merely add technological complexity.

Discussion

The prostaglandin model provides a coherent explanation for the clinical effectiveness of anti-inflammatory therapy in primary dysmenorrhea. It also explains why timing matters. NSAIDs are most rational when used before or at the beginning of prostaglandin surge, rather than after severe pain has fully developed.

However, prostaglandins are not the only determinants of symptoms. Vasopressin, leukotrienes, central sensitization, psychological stress, sleep disturbance, and secondary pathology may influence clinical response. Therefore, persistent pain despite correct NSAID use should trigger clinical reassessment rather than repeated dose escalation.

Real-world evidence can improve NSAID stewardship. E-prescription systems can show which drugs are used, how often therapy is repeated, whether gastroprotection is added, and when patients switch to hormonal therapy. Pharmacovigilance can identify adverse reaction patterns, while AI can support risk stratification if properly validated.

Global regulatory and ethical context

International regulatory science increasingly recognizes RWD and RWE as important complements to traditional clinical trials. The FDA has developed programs and guidance around the use of RWD and RWE in regulatory decision-making, particularly for post-marketing safety and effectiveness questions. EMA's DARWIN EU initiative illustrates a European model for federated real-world data analysis, in which evidence can be generated from multiple data partners while preserving governance standards.

WHO guidance on artificial intelligence in health emphasizes ethics, transparency, human oversight, equity, data protection, and accountability. These principles are directly relevant to menstrual health because reproductive data are sensitive and because algorithmic systems may reproduce existing gender, socioeconomic, linguistic, or documentation bias. An AI model that



underestimates pain in groups who seek care less frequently would worsen inequity rather than improve care.

Explainable AI is not a decorative requirement; it is a clinical safety condition. Clinicians need to know whether a model recommends referral because of progressive pain, repeated treatment failure, abnormal bleeding, or a pattern suggesting secondary dysmenorrhea. Ethical AI also requires clear consent, data minimization, audit trails, local validation, and mechanisms for correcting erroneous outputs.

Clinical decision support systems should be evaluated not only for accuracy but also for workflow fit. A technically accurate alert that appears too late, interrupts routine care, or produces too many false positives will be ignored. The best systems provide short, specific recommendations at the point of decision: optimize NSAID timing, screen for contraindications, ask about red flags, consider hormonal therapy, or refer for suspected endometriosis.

Uzbekistan-specific considerations

Uzbekistan's phased development of electronic prescriptions and digital health infrastructure can support safer analgesic use. For dysmenorrhea, structured recording of pain severity, NSAID timing, adverse effects, and referral criteria would enable national RWE studies and improve clinical governance.

Clinical pharmacology services should contribute to patient leaflets, physician algorithms, pharmacist counseling, and pharmacovigilance workflows. Menstrual health education can reduce unsafe self-medication and encourage timely consultation for red flags.

Critical interpretation of NSAID evidence

NSAIDs are often described as first-line therapy, but this statement is incomplete unless the clinical conditions for effectiveness are specified. The intervention is not merely the tablet; it is the correct patient, correct diagnosis, correct timing, correct dose, and correct monitoring. This matters because real-world failure is frequently behavioral or organizational rather than pharmacological. Patients may take the drug too late, use too low a dose, stop after one tablet, or combine multiple products without understanding that they share the same mechanism.

The evidence from controlled trials supports NSAID benefit, but trials cannot fully reproduce the context of monthly self-management. In practice, a patient may wake with severe pain, delay medication because of school or work, take the drug without food, vomit, or avoid a second dose because of fear of adverse effects. These details can determine whether anti-inflammatory therapy appears successful. Therefore, effectiveness research should measure timing and adherence with the same seriousness as drug choice.

The category of NSAIDs is pharmacologically diverse. Differences in half-life, dosing schedule, gastrointestinal tolerability, patient familiarity, cost, and availability influence real-world use. A medication with strong efficacy but inconvenient dosing may be less effective in routine care than a slightly less potent but more acceptable option. Shared decision-making should therefore include practical feasibility, not only theoretical potency.

Safety should be discussed without exaggeration and without minimization. Short intermittent courses are appropriate for many patients, but repeated monthly use over years is not trivial. Young age does not eliminate gastrointestinal, renal, hypersensitivity, or interaction risks. Clinical



screening is especially important in patients with asthma triggered by aspirin, kidney disease, dehydration risk, anticoagulant use, peptic ulcer history, or possible pregnancy.

NSAID stewardship should also address public misunderstanding. Some patients believe stronger pain requires combining several analgesics. Others avoid all medication and endure severe pain because they fear dependency, although NSAIDs are not opioids. Clear counseling can prevent both unsafe overuse and unnecessary undertreatment.

Analytical design for future real-world studies

A strong real-world study of NSAID effectiveness in primary dysmenorrhea should emulate a target trial. Eligibility would include patients with suspected primary dysmenorrhea and no red flags at baseline. Treatment strategies might compare early scheduled NSAID use, delayed rescue NSAID use, NSAID plus heat therapy, or hormonal therapy after inadequate response. Time zero should be clearly defined, for example the first documented dysmenorrhea visit or first e-prescription. Follow-up should occur across several cycles.

Outcomes should include pain reduction, functional recovery, missed school or work, reconsultation, therapy switching, adverse drug reactions, and referral for suspected secondary dysmenorrhea. Confounders should include baseline severity, age, bleeding intensity, comorbidity, previous medication exposure, access to care, and contraindications. Propensity score methods can reduce measured confounding, but unmeasured factors such as stigma, family support, and over-the-counter use may remain.

Survival analysis can answer clinically relevant questions. Kaplan-Meier curves could estimate time to treatment switching or time to gynecological referral. Cox regression could model predictors of persistent symptoms. Competing risks may be relevant when patients discontinue therapy for pregnancy, contraception preference, adverse effects, or loss to follow-up. Missing data should be handled transparently rather than ignored.

Patient-reported data are essential. Without pain diaries or mobile reporting, researchers may misinterpret prescription refills as successful treatment when the patient is actually purchasing additional over-the-counter medication. Conversely, lack of refill may mean symptom resolution, adverse effects, cost barrier, or abandonment of care. Real-world studies should therefore combine clinical records with patient-reported outcomes whenever possible.

Table 3. Target trial emulation outline for NSAID effectiveness

Component	Operational definition	Bias addressed
Eligibility	Suspected primary dysmenorrhea without red flags	Disease misclassification
Time zero	First documented treatment decision	Immortal time bias
Strategies	Early scheduled NSAID vs delayed rescue use	Exposure ambiguity
Outcomes	Pain, function, switching, adverse reactions	Narrow endpoint bias
Adjustment	Severity, age, bleeding, comorbidity, access	Confounding by indication



Clinical pharmacology and pharmacogenetic horizon

Clinical pharmacology can make primary dysmenorrhea treatment safer and more rational. A pharmacology-informed protocol would include contraindication screening, dose limits, food and hydration advice, interaction checks, patient education, and documentation of adverse effects. It would also define when treatment failure is real: inadequate benefit despite early, adequate, repeated use across cycles and absence of major adherence problems.

Pharmacogenetic research may eventually identify patients at higher risk of adverse reactions or altered NSAID metabolism. However, current routine care should not wait for genetic testing. Most preventable problems can be addressed through history, medication reconciliation, dose education, and follow-up. Precision medicine should be understood as the right level of personalization for the available evidence, not necessarily as high-cost molecular testing.

Biomarkers of prostaglandin activity, inflammatory phenotype, or pain sensitization may help future studies, but they must be linked to clinical decisions. A biomarker that predicts severe pain but does not change treatment is scientifically interesting but clinically limited. The most useful biomarkers would identify patients unlikely to respond to NSAIDs, patients likely to have secondary pathology, or patients at increased risk of adverse effects.

Uzbekistan: NSAID stewardship and digital health

In Uzbekistan, a practical NSAID stewardship program for dysmenorrhea could be implemented through primary care, gynecology clinics, pharmacies, and student health services. The program would standardize counseling, contraindication screening, adverse reaction reporting, and referral criteria. It would also reduce unsafe self-medication by explaining that multiple NSAIDs should not be combined without medical advice.

E-prescription data can identify repeated monthly use, high-dose patterns, switches between NSAIDs, and co-prescriptions that increase risk. If linked with adverse reaction reporting, these data can support local pharmacovigilance. If linked with clinical outcomes, they can support effectiveness research. The same infrastructure could also identify patients repeatedly treated for pain without evaluation for secondary causes.

AI should be introduced only after data quality improves. A simple rule-based clinical decision support tool may be more useful initially than a complex black-box model. For example, the system can remind clinicians to ask about red flags, document contraindications, and schedule follow-up after several cycles. More advanced machine learning models can be developed later when reliable longitudinal data are available.

The national research agenda should include adolescent menstrual health, over-the-counter analgesic behavior, school absenteeism, NSAID safety, delayed diagnosis of endometriosis, and culturally adapted patient education. These topics are feasible, clinically relevant, and directly connected to everyday practice.

Conclusion

Primary dysmenorrhea is strongly linked to increased prostaglandin production, uterine hypercontractility, vasoconstriction, ischemia, and nociceptive activation. NSAIDs are therefore pathogenetically justified first-line therapy when used early, correctly, and safely.



The future of anti-inflammatory therapy in primary dysmenorrhea should combine molecular understanding, patient education, real-world evidence, pharmacovigilance, AI-assisted prediction, and individualized safety assessment. Digital health reforms may allow Uzbekistan to generate its own menstrual health evidence and improve rational NSAID use.

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