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Research Article

Pharmacovigilance in Monitoring of Ibuprofen

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ABSTRACT

Pharmacovigilance is the science and set of activities aimed at identifying, assessing, understanding, and preventing adverse effects or any other drug-related issues. This proactive approach helps in the early detection of safety signals, enabling swift regulatory actions to protect public health. The pharmacovigilance process includes:

1. Detecting and reporting adverse events
2. Identifying and evaluating signals
3. Assessing and mitigating risks
4. Ensuring regulatory compliance and reporting

INTRODUCTION

Pharmacovigilance is the study and use of medication safety monitoring with the goal of detecting, evaluating, and averting side effects or other drug-related issues. Pharmacovigilance is essential when it comes to the menstrual cycle since it guarantees that drugs, particularly hormone therapies, contraceptives, and treatments for menstrual diseases, are safe and effective for people at all stages of the cycle. Fluctuations in hormone levels throughout the menstrual cycle can influence how drugs are metabolized and how individuals respond to them. Additionally, certain medications may impact the cycle itself, causing changes in flow, timing, or symptoms such as pain and mood swings. Monitoring these effects is essential, particularly for populations such as adolescents, those with underlying gynecological conditions (like PCOS or endometriosis), or individuals undergoing hormone therapy. Effective pharmacovigilance in this area ensures early detection of side effects, enhances patient education, and informs safer, more personalized treatment strategies.

History of Pharmacovigilance:

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The origin of pharmacovigilance dates back to the 1960s, when the thalidomide tragedy underscored the need for better drug safety monitoring. Since then, pharmacovigilance has developed into a vital part of the healthcare system. [1][2][3]

Definition

The science and practice of monitoring the safety of medicines and vaccines and preventing or reducing their adverse effect. It involves collecting and analyzing data on the safety of medicine and taking action to improve their safety and benefits.

Pharmacovigilance involves:

- Collecting data about problems caused by drugs.
- Analyzing data to find ways to prevent adverse events.

Examples of pharmacovigilance include:

- Drug safety surveillance
- Drug abuse and adverse effect[4]

Menstrual Cycle

A menstrual cycle begins with menstruation, when the lining of your uterus is shed. This process is part of your reproductive system and prepares your body for a potential pregnancy. A typical cycle usually lasts between 24 and 38 days.

Menstruation:

Menstruation is the monthly process of shedding the uterine lining. It's also referred to as a period, menstrual cycle, or menses. During menstruation, menstrual blood, which is a mix of blood and tissue from the inside of your uterus, flows from your uterus, through your cervix, and out of your body via the vagina.Menstruation is regulated by hormones, which are chemical signals produced by your pituitary gland (in your brain) and ovaries (part of your reproductive system). These hormones are released at specific times during the menstrual cycle. They cause the uterine lining to thicken in preparation for a potential pregnancy, allowing an egg to implant if fertilization occurs. The hormones also trigger ovulation, when an egg is released from the ovaries and moves through the fallopian tubes, waiting for sperm. If fertilization doesn't happen, the egg is not implanted, and the uterine lining breaks down and sheds, resulting in your period.

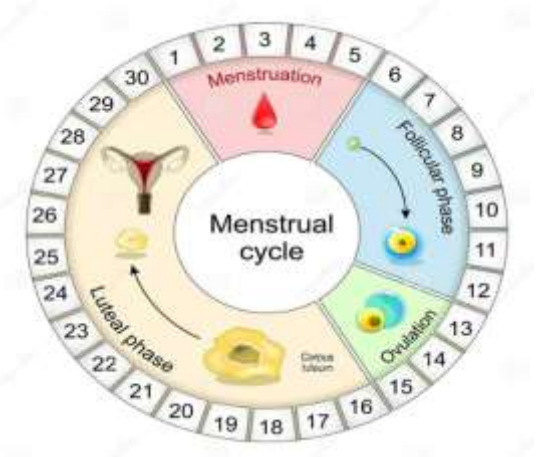
Four phases of the menstrual cycle

The menstrual cycle is driven by the rise and fall of hormones, which cause various responses in the reproductive organs. These phases include:

- **The Menses Phase:** This phase starts on the first day of your period when the uterine lining sheds if pregnancy hasn't occurred. Most people bleed for 3 to 5 days, although periods lasting anywhere from 3 to 7 days are usually normal.
- **The Follicular Phase:** This phase overlaps with the menses phase and lasts until ovulation. Estrogen levels rise, prompting the uterine lining to thicken. Meanwhile, follicle-stimulating hormone (FSH) stimulates follicles in the ovaries to grow. Between days

10 to 14, one follicle will mature into a fully developed egg (ovum).

- **Ovulation:** This phase happens around day 14 in a typical 28-day cycle. A surge in luteinizing hormone (LH) triggers the release of the egg from the ovary, marking ovulation.
- **The Luteal Phase:** From day 15 to day 28, the egg travels through the fallopian tubes toward the uterus. Progesterone levels rise to prepare the uterine lining for potential pregnancy. If the egg is fertilized and implants in the uterus, pregnancy occurs. If not, estrogen and progesterone levels drop, and the uterine lining sheds during your period.[5]



Drug Profile:

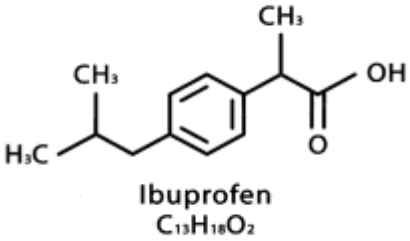
Most Common Drug Used in Menstrual Cycle

Drug Name	Uses
Ibuprofen / Naproxen	Relieves menstrual cramps (dysmenorrhea)
Mefenamic Acid	Reduces pain and blood loss during menstruation
Tranexamic Acid	Reduces heavy menstrual bleeding (menorrhagia)
Combined Oral Contraceptives	Regulates cycles, reduces bleeding & pain
Medroxyprogesterone Acetate	Treats irregular periods, induces withdrawal bleed
Norethisterone	Delays or regulates periods
GnRH Agonists (e.g., Elagolix)	Treats endometriosis & fibroids
LNG-IUS (e.g., Mirena)	Long-term control of heavy bleeding
Clomiphene Citrate	Induces ovulation in PCOS or infertility cases

From all above drug, **Ibuprofen** is the most widely used drug during menstruation. [6][7]

Ibuprofen

A medication used to reduce fever, pain, inflammation, menstrual cramps and also slow down heavy periods.



Brand Name: Advil, Addaprin

Generic Name: Ibuprofen

Chemical FormulaC13H18O2

Synonyms: Ibuprofen, Ibuprofene, Ibuprofeno.

Therapeutic Categories: Anti Inflammatory Agent, Non-steroidal [27]

MOA:

Here's how it works:

- It inhibits the cyclooxygenase (COX) enzymes, mainly COX-1 and COX-2.
- These enzymes are involved in the production of prostaglandins, which are hormone-like substances that:

- Trigger uterine muscle contractions.
- Contribute to inflammation and pain during menstruation.

During menstruation:

- The endometrium (lining of the uterus) releases prostaglandins.
- High levels of prostaglandins lead to stronger uterine contractions, which can cause cramping (dysmenorrhea) and pain.
- Ibuprofen reduces prostaglandin levels, which:
- Decreases uterine contractions.
- Reduces cramping and pain.
- May also help reduce menstrual blood flow, since prostaglandins promote Vasodilation and blood vessel permeability.
- So overall, ibuprofen helps manage menstrual pain and heavy bleeding by blocking prostaglandin production.[8]

Pharmacology of Ibuprofen:

The pharmacology of ibuprofen in the menstrual cycle, particularly in the treatment of primary dysmenorrhea, involves both its pharmacokinetics and pharmacodynamics:

1. Pharmacodynamics (How Ibuprofen Affects the Body)

- **Class**: Nonsteroidal Anti-Inflammatory Drug (NSAID)
- **Mechanism of Action:**
- Ibuprofen is a non-selective inhibitor of cyclooxygenase (COX-1 and COX-2) enzymes.
- It prevents the conversion of arachidonic acid to prostaglandins by blocking the COX enzymes.

Prostaglandins (especially PGF2α and PGE2) are elevated during menstruation, contributing to uterine contractions, pain, and inflammation.

- By lowering prostaglandin levels, ibuprofen helps reduce uterine contractions, ischemia, and menstrual pain.
- **Clinical Effects:**
- Alleviates menstrual cramps (dysmenorrhea).
- May reduce menstrual blood loss by promoting vasoconstriction and limiting endometrial shedding.

2. Pharmacokinetics (How the Body Processes Ibuprofen)

- **Absorption**: Rapid oral absorption, with peak plasma concentrations reached within 1–2 hours.
- **Distribution**: Widely distributed throughout the body, with 99% protein binding.
- **Metabolism**: Processed in the liver via oxidation.
- **Excretion**: Primarily eliminated by the kidneys as inactive metabolites.
- **Half-Life**: Approximately 2–4 hours (making it a short-acting NSAID).

3. Dosage for Dysmenorrhea

- **Common Dosage**: 200–400 mg every 4–6 hours, starting at the onset of menstrual pain or bleeding.

- **Optimal Timing**: Best taken early in the menstrual cycle, as soon as symptoms begin, to maximize efficacy.

1. Drug Classification

- **Class**: Non-Steroidal Anti-Inflammatory Drug (NSAID)
- **Subclass**: Propionic acid derivative
- **Generic Name**: Ibuprofen

2. Dosage for Menstrual Pain

- **Adults**: 200–400 mg orally every 4–6 hours as needed.
- **Maximum Daily Dose:**
  - Over-the-counter (OTC): 1200 mg
  - Under medical supervision: Up to 2400 mg
- **Best Efficacy**: Taken at the onset of menstruation or cramping to reduce prostaglandin synthesis early.

3. Drug Interactions

- **Other NSAIDs**: Increases the risk of gastrointestinal bleeding.
- **Anticoagulants** (e.g., warfarin): May enhance the risk of bleeding.
- **Antihypertensive (ACE inhibitors/ARBs)**: May reduce their effectiveness and worsen kidney function.
- **Corticosteroids**: Additive gastrointestinal toxicity.

Monitoring Drug Safety and Adverse Effects of Ibuprofen:

When ibuprofen is used to manage menstrual cycle symptoms (such as menstrual cramps), monitoring its safety and potential adverse effects is still important, especially since it's often used in the short term but can be taken frequently during menstruation. Here's how to monitor for safety and adverse effects in this context:

1. Gastrointestinal (GI) Side Effects

Monitoring:

- Watch for symptoms such as stomach pain, indigestion, nausea, or vomiting (especially if blood is present).
- Look out for signs of gastrointestinal bleeding like black, tarry stools or vomit that looks like coffee grounds.

Adverse effect:

1. Stomach Ulcers and Bleeding: Ibuprofen can irritate the stomach lining, increasing the risk of ulcers and gastrointestinal bleeding, especially with prolonged use.
2. Nausea and Vomiting: Some individuals may experience nausea or vomiting as a side effect.
3. Indigestion and Heartburn: Common symptoms include indigestion and heartburn.

Kidney Function

Monitoring:

For individuals using ibuprofen every cycle, watch for symptoms of kidney issues like swelling in the legs or ankles, fatigue, or reduced urine output.

Adverse effect:

Kidney Damage: High doses or prolonged use of ibuprofen can impair kidney function, leading to potential kidney damage.

2. Cardiovascular Risks

Monitoring:

- Keep an eye on blood pressure, especially for those with a history of hypertension or heart disease.
- Watch for signs of fluid retention or swelling, which could indicate cardiovascular stress.

Adverse effect:

1. Increased Blood Pressure: Regular use of NSAIDs like ibuprofen may elevate blood pressure.
2. Heart Attack and Stroke: There is a potential increased risk of heart attack and stroke with long-term use.

3. Allergic Reactions

Monitoring:

Be vigilant for any signs of an allergic reaction, particularly shortly after taking ibuprofen, such as rashes, itching, or swelling.

Adverse effect:

1. Anaphylaxis: Severe allergic reactions, though rare, can occur, leading to symptoms like difficulty breathing and swelling.

4. Liver Function

Monitoring:

Be mindful of any symptoms that could indicate liver issues, such as fatigue, dark urine, or jaundice.

Adverse effect:

1. Liver Dysfunction: Rarely, ibuprofen can cause liver issues, including jaundice and elevated liver enzymes.

5. Drug Interactions

Monitoring:

- Keep track of any other medications you are taking (e.g., birth control, blood pressure medication) and their potential interactions with ibuprofen.
- Watch for unusual bruising or bleeding if using ibuprofen with other medications.

Adverse effect:

Some medications can interfere with the menstrual cycle, causing changes in bleeding patterns, cycle length, and even leading to missed or irregular periods

6. Overuse and Tolerance

Monitoring:

- Avoid using ibuprofen frequently across multiple menstrual cycles unless necessary.
- If the menstrual cramps become progressively more difficult to manage with ibuprofen, consult a healthcare provider for alternative treatments or evaluations.

Adverse effect:

- Headaches
- Dizziness
- Nausea and vomiting
- Heartburn
- Indigestion

7. Reproductive and Hormonal Effects

- Menstrual Irregularities: Excessive use of ibuprofen has been associated with menstrual irregularities, including delayed periods.
- Delayed Ovulation: High doses may interfere with ovulation, potentially affecting fertility.

8. Neurological and Sensory Effects

- Dizziness and Headache: Some individuals may experience dizziness or headaches.

- Tinnitus: Ringing in the ears (tinnitus) can occur in rare cases.

9. Dermatological Reactions

Skin Rash and Itching: Allergic reactions may manifest as skin rashes or itching. Photosensitivity: Increased sensitivity to sunlight, leading to rashes or sunburns. [9][10]

EXPERIMENTAL WORK:

Experimental Work on Pharmacovigilance in Menstrual Cycle: Ibuprofen

The study of pharmacovigilance in the context of Ibuprofen (a non-steroidal anti-inflammatory drug, NSAID) and its effects across different phases of the menstrual cycle can provide valuable insights into how hormonal fluctuations influence the drug's pharmacokinetics, pharmacodynamics, and potential adverse effects.

Case Study: We monitored following patients which shows adverse effects such as:

Patient Profile:

Case 1:

Name: Payal Navnath Ugale

Age: 23

Occupation: University Student

Address: A/P. Vadner Bhairav, Tal- Chandwad, Dist- Nashik 422209.

Menstrual History: Regular 28-day cycle, bleeding lasts 4–5 days

Chief Complaint: Severe lower abdominal cramps during the first two days of menstruation.

Medication History:

Ibuprofen Use:

- 400 mg every 6 hours on Day 1 and Day 2 of her period
- Has been using this dose regularly for 2 years
- Sometimes takes it on an empty stomach due to a busy class schedule

Side Effects Experienced:

- Recurrent, epigastric pain(upper stomach discomfort)
- Occasional heartburn.
- Felt dizzy and fatigued on Day 2 of her period
- Black stools, observed once, which resolved on its own
- No known kidney, liver, or cardiac conditions

Assessment:

- Likely NSAID-related gastritis
- Potential warning sign of GI bleeding (black stools)
- No known allergies to NSAIDs

Prevention and Management Plan:

1. Modify Ibuprofen Use

- Reduced to 200 mg every 6–8 hours as needed, only on the first two days of menstruation
- Limit use to 2 consecutive days per cycle
- Maximum daily dose: 600 mg (vs. 1200 mg OTC limit)

2. Always Take With Food

- Advised to take ibuprofen only after breakfast or a meal.
- Kept snacks in her bag for college to avoid taking it on an empty stomach.

3. Add Gastro protection

Prescribed pantoprazole 40 mg once daily during menstruation (or while taking ibuprofen) to reduce acid production and protect stomach lining.

4. Hydration and Lifestyle

- Encouraged to drink at least 2 liters of water per day, especially during her period.
- Avoided caffeinated and acidic drinks (coffee, citrus juice) while on ibuprofen.

5. Avoid Alcohol and Smoking

She occasionally consumed alcohol on weekends advised to avoid alcohol during her period and while on ibuprofen.

6. Alternative Pain Management

- Added heat therapy (hot water bag for 15–20 minutes) and yoga stretches for pelvic pain.
- Introduced magnesium-rich foods (dark leafy greens, nuts, and bananas) into her diet.

6. Follow-Up and Monitoring

Regular follow-up in 3 months to assess:

- Frequency of cramps
- Need for ibuprofen
- Any recurrence of GI symptoms
- If symptoms persisted, referral to a gynecologist for evaluation of secondary causes (e.g., endometriosis)

Outcome:

After 3 months, Payal reported:

- Less frequent ibuprofen use
- No further stomach pain or black stools
- Better overall management of cramps using a combined approach of medication and lifestyle change.

Prescribe by: Dr. Shraddha Sopan Kute

Hospital name: Pearls Women Clinic

Address: 3, Sharmila appartment, Gangapur Rd, Budha halwai, Old Gangapur naka, Nashik, Maharashtra, 422001.

Case 2:

Name: Nita Pramod Deshmukh Age: 29

Profession: Software Engineer

Address: A/P. Baragaon, Tal- Sinner, Dist-Nashik 422103.

Menstrual History: 30-day regular cycle, mild-to-moderate cramps for 2 days

Ibuprofen Use: 400 mg 1–2 times per day, every month for the last 5 years

Complaints:

- No severe symptoms, but recently experienced bloating and intermittent stomach discomfort
- Started feeling reliant on ibuprofen for even mild cramps

Assessment:

- Overuse of ibuprofen for mild symptoms.
- Mild gastritis likely due to long-term NSAID use.

Prevention Steps:

1. Reduced dose to 200 mg only when pain is moderate.
2. Skipped ibuprofen when cramps are mild – switched to heat patches and gentle abdominal massage.
3. Advised to take ibuprofen with yogurt or meals.
4. Added ginger tea and hydration during her period to ease cramps naturally.

5. No need for gastro protective drugs yet, but advised regular review.

RESULT:

Ibuprofen drug are used to reduce menstrual cramps and also reduce prostaglandin production. Less prostaglandin means less uterine shedding, leading to fewer cramps and less bleeding. But according to the above patients we monitor that ibuprofen drug also shows most common adverse effects such as Stomach pain, Heartburn, Vomiting, Feels dull, dizziness, mild dehydration, shortness in breath, black stools, swelling in legs, fatigue, nausea and unusual weight gain. So, we monitored between age 16 to 45 year old, for 40 patients (Female) which revealed adverse effect like diarrhea in age groups between 21 to 30 year old female.

CONCLUSION:

Ibuprofen is an effective no steroidal anti-inflammatory drug (NSAID) commonly used to relieve menstrual pain (dysmenorrhea). It works by reducing the production of prostaglandins, hormone-like substances that cause uterine contractions and pain during menstruation. When taken as directed, ibuprofen can significantly lessen menstrual cramps and associated discomfort. However, prolonged or excessive use may lead to gastrointestinal or kidney issues, so it should be used responsibly and under medical guidance if symptoms persist or worsen.

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