Dysmenorrhea

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Primary vs Secondary

For clinical purposes, dysmenorrhea is divided into two broad categories:

- **Primary dysmenorrhea** refers to the presence of recurrent, crampy, lower abdominal pain that occurs during menses in the absence of demonstrable disease that could account for these symptoms.
- **Secondary dysmenorrhea** has the same clinical features, but occurs in women with a disorder that could account for their symptoms.
Primary Dysmenorrhea

- Onset in adolescence, at or shortly after (6–24 months) menarche
- Clear, predictable temporal pattern, beginning just before or at the start of menstruation

<table>
<thead>
<tr>
<th>Lasts for 8-72 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most severe during the 1st &amp; 2nd day</td>
</tr>
<tr>
<td>Frequently radiates to back and thighs</td>
</tr>
<tr>
<td>Systemic symptoms (eg, N, V, D, fatigue)</td>
</tr>
</tbody>
</table>
Secondary Dysmenorrhea

- Originates from a number of identifiable pathological conditions

<table>
<thead>
<tr>
<th>Onset can occur at any time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset typically &gt; 2 yrs after menarche</td>
</tr>
<tr>
<td>Accompanied by other gynecologic symptoms</td>
</tr>
<tr>
<td>Timing &amp; intensity during menses can be variable</td>
</tr>
</tbody>
</table>
Secondary Dysmenorrhea: Endometriosis
Secondary Dysmenorrhea: Adenomyosis
Secondary Dysmenorrhea: Leiomyoma
Secondary Dysmenorrhea: Endometrial polyp
Secondary Dysmenorrhea: Pelvic adhesions
Secondary Dysmenorrhea: Mullerian anomalies
Prevalence of Primary Dysmenorrhea

- 50-90% of women worldwide
- 10-25% of reproductive women have severe dysmenorrhea
- World Wide: the most common gynecologic disorder
Risk factors

- BMI (conflicting reports)
- smoking
- younger (earlier) menarche
- heavy or long menstrual flow
- familial history
- alcohol consumption
- nulliparity
Risk factors

- BMI (conflicting reports)
- smoking
- younger (earlier) menarche
- heavy or long menstrual flow
- familial history
- alcohol consumption
- nulliparity
Dysmenorrhea is inextricably linked to prostaglandins

Prostaglandins (PGs)

- Ubiquitously distributed intracellular substances
- Significant biological effects on a wide variety of physiological as well as pathological activities
Prostanoids

➢ Three main groups
  ○ prostaglandins
  ○ prostacyclins
  ○ thromboxanes

Dysmenorrhea
Prostaglandins
Prostaglandins

- All women have increased levels of PGs during the luteal phase
- High progesterone levels tend to stabilize endometrial lysosomes
- Falling levels of progesterone levels labilize lysosome activity
- Increasing lysosomal activity $\rightarrow$ increases PGs
- The myometrium is highly responsive to PGs
### Dysmenorrhea / PGs

<table>
<thead>
<tr>
<th><strong>Higher circulating levels of PGs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Higher endometrial levels of PGs</strong></td>
</tr>
<tr>
<td><strong>PGs levels are highest in the first 48 hr of menses</strong></td>
</tr>
<tr>
<td><strong>Severity of dysmenorrhea directly correlated with PG levels</strong></td>
</tr>
<tr>
<td><strong>Clinical administration of PGs results in symptoms of dysmenorrhea</strong></td>
</tr>
</tbody>
</table>
Pathogenesis

➢ Overproduction of uterine PGs
➢ Enhanced release of PGs, from disintegrating cells during endometrial sloughing causes myometrial hypercontractility
Dysmenorrheic uterine contractions

- Nonrhythmic
- Occur at high frequency (>4-5/10 min)
- Often begin from an elevated basal tone
- Result in high intrauterine pressures

- **frequently > 150 mm Hg**
- **occasionally > 400 mm Hg**
Dysmenorrhea

Uterine pressure > Arterial pressure

- Anaerobic metabolites accumulate
- Stimulation / activation of type C pain neurons
- Uterine ischemia

Ischemia

Hypoxemia

myometrial cells

PAIN
Dysmenorrhea

↑ Sensitivity to Pain (widespread & long-lasting)

Unknown Genetic/Environmental Factors

Recurrent Menstrual Pain

CNS Changes:
- Pain-induced central activity
- Cerebral metabolism
- Cerebral structure

↓ Quality of Life
↓ Sleep Quality
↓ Physical Activity
Poorer Mood
Co-morbidity with CPP

Predisposition to Chronic Pain?
Dysmenorrhea

![Diagram showing the role of prostaglandins in dysmenorrhea](image)
Dysmenorrhea

Cell membrane phospholipids

Phospholipase A₂

Arachidonic acid

Cyclooxygenase pathway

Lipoxygenase pathway

Leukotrienes (inflammatory sites)

Inflammation

Prostaglandins
Dysmenorrhea

Prostaglandins
Dysmenorrhea

Cell membrane phospholipids

Phospholipase A₂

Arachidonic acid

Cyclooxygenase pathway

COX-1 (physiologic)

Lipoxygenase pathway

Leukotrienes
(inflammatory sites)

Inflammation
Cyclooxygenase

Officially: prostaglandin-endoperoxide synthase (PTGS)

Converts arachidonic acid to PGs

“COX” (abbreviation already used for cytochrome oxidase)
Dysmenorrhea
Dysmenorrhea

Cell membrane phospholipids

Phospholipase A₂

Arachidonic acid

Cyclooxygenase pathway

COX-1 (physiologic)

Leukotrienes (inflammatory sites)

Inflammation

Lipoxygenase pathway

COX-2 (inducible)
Dysmenorrhea

Cell membrane phospholipids

Phospholipase $A_2$

Arachidonic acid

COX-1 (physiologic)

Prostaglandins, thromboxane
(stomach, intestine, kidney, platelets)

COX-2 (inducible)

Lipoygenase pathway

Leukotrienes (inflammatory sites)
Inflammation
Dysmenorrhea

Cell membrane phospholipids

Phospholipase A₂

Arachidonic acid

COX-1 (physiologic)
Prostaglandins, thromboxane
(stomach, intestine, kidney, platelets)

COX-2 (inducible)
Prostaglandins
(inflammatory sites, macrophages, synovocytes)
Inflammation, pain, and fever

Lipoxygenase pathway

Leukotrienes (inflammatory sites)

Inflammation
Dysmenorrhea

Cell membrane phospholipids

Phospholipase A2

Arachidonic acid

COX-1 (physiologic)

COX-2 (inducible)

Lipoxygenase pathway

Leukotrienes (inflammatory sites)

Inflammation

Older NSAIDs

Prostaglandins, thromboxane
(stomach, intestine, kidney, platelets)

Prostaglandins
(inflammatory sites, macrophages, synovocytes)

Inflammation pain and fever

Dysmenorrhea
Dysmenorrhea

Cell membrane phospholipids

Phospholipase $A_2$

Arachidonic acid

COX-1 (physiologic)

COX-2 (inducible)

newer NSAIDs

Prostaglandins, thromboxane
(stomach, intestine, kidney, platelets)

Leukotrienes (inflammatory sites)
Inflammation

Prostaglandins
(inflammatory sites, macrophages, synovocytes)

Inflammation pain and fever

Lipoxygenase pathway

Dysmenorrhea
Dysmenorrhea

Cell membrane phospholipids

Phospholipase $A_2$

Arachidonic acid

[Pathway diagram]

COX-1 (physiologic)

Prostaglandins, thromboxane
(stomach, intestine, kidney, platelets)

newer NSAIDs

COX-2 (inducible)

Prostaglandins
(inflammatory sites, macrophages, synovocytes)

Leukotrienes
(inflammatory sites)

Inflammation pain and fever

Lipoxygenase pathway

Dysmenorrhea
Primary Dysmenorrhea: Treatment

- NSAID -
  - decrease PG production

- OCP
  - decrease endometrial volume
  - stabilize endometrial lysosomal activity

- Abdominal heat wrap

- Alternative medical therapies
  - Traditional Chinese Medicine
Primary Dysmenorrhea: Treatment

Secondary interventions - medical

➢ GnRH agonist (e.g., leuprolide acetate (Lupron))
➢ Long acting progestins (e.g., DMPA, (Depo-Provera)
➢ Etonogestrel (Implanon, Nexplanon)
➢ Intra-uterine device (Mirena) *
Primary Dysmenorrhea: Treatment

Secondary interventions - surgical

- Transcutaneous nerve stimulation
- Uterosacral nerve ablation
- Presacral neurectomy
Primary Dysmenorrhea: Treatment

NSAID synonymous with

- Cyclooxygenase inhibitor
- Prostaglandin synthetase inhibitor
- COX 1
- COX 2
### NSAID

- **Globally one of the most freq. prescribed drugs**
- **Various formulations show similar efficacy**
- **Pain relief ~ 64 - 100%**
- **~15% of women do not respond or are intolerant**
FDA Advisory in 2004

➢ Physicians should closely evaluate each patient's risk for cardiovascular events (such as heart attack and stroke) when making decisions about using NSAIDs and COX-2 inhibitor drugs.

➢ Some patients with a high risk of gastrointestinal problems, who have a history of intolerance to non-selective NSAIDs (e.g. NSAIDs other than COX-2 inhibitors), or who have not had good results with non-selective NSAIDs may be the most appropriate patients to continue using COX-2 inhibitors Celebrex or Bextra.

➢ Patients should be well-advised to follow label directions for over-the-counter pain medications and NSAIDs (e.g. Aleve or brands of ibuprofen), being sure not to use longer than 10 days in a row without consulting a physician. Patients should also be sure not to take a higher dosage of Aleve or other NSAIDs than what is recommended on the label. In a separate statement, the FDA also recommended that patients taking Celebrex should take the lowest effective dose in order to avoid overuse.
Secondary Dysmenorrhea

➢ Lower abdominal pain that occurs during menses in the absence of demonstrable disease that could account for these symptoms.
➢ Occurs in women with a disorder that could account for their symptoms, such as endometriosis, adenomyosis, or uterine fibroids.
Secondary Dysmenorrhea: Treatment

Treatment of the underlying (etiologic) cause

- Endometriosis
- Adenomyosis
- Leiomyoma
- Endometrial polyps
- Pelvic adhesions
- Obstructive mullerian anomalies
- Cervical stenosis
Dysmenorrhea: evaluation

- Thorough history
- Physical examination
- Pelvic examination
  - speculum examination
  - bimanual examination
  - rectal examination
Dysmenorrhea: evaluation

Endometriosis can be associated with lateral displacement of the cervix
**Dysmenorrhea**

**Medical history**

- History of primary dysmenorrhea
  - No previous diagnosis of pelvic pathology
  - Menstrual-associated cramping in lower abdomen

**Pain:**
- Onset: 6 – 24 months after menarche
- Has a predictable temporal pattern (just before/and or during menstruation)
- Typically lasts for 8 – 72 h
- May radiate to back and thighs
- May be accompanied by systemic symptoms e.g. diarrhea, vomiting

**No history of primary dysmenorrhea:**
- Pain onset: > 2 years after menarche
- Irregular menstrual cycles
- Pain during non-menstrual phases of the menstrual cycle
- May have other symptoms e.g. menorrhagia and intermenstrual bleeding

**Physical Examination**

- No pelvic pathology
- Pelvic pathology

**Primary dysmenorrhea**

**Secondary dysmenorrhea**
Dysmenorrhea Dilemma

Lupron vs Laparoscopy
Dysmenorrhea

↑ Sensitivity to Pain
(widespread & long-lasting)

Unknown Genetic/Environmental Factors

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- Cerebral structure

↓ Quality of Life
↓ Sleep Quality
↓ Physical Activity
Poorer Mood
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Predisposition to Chronic Pain?
Questions
Cytotec (misoprostol)

PGE1

a synthetic analog of PGE1

Cervidil (dinoprostone)

PGE2
Dysmenorrhea

Hemabate
(Carboproast)
PGF2α
MIRENA (levonorgestrel-releasing intrauterine system)
Initial U.S. Approval: 2000

--------------------------RECENT MAJOR CHANGES--------------------------
Dosage and Administration (2) 05/2014
Warnings and Precautions (5.6) 02/2013

------------------------INDICATIONS AND USAGE------------------------
Mirena is a progestin-containing intrauterine system indicated for:
• Intrauterine contraception for up to 5 years (1)
• Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception. (1)
It is recommended for women who have had at least one child.
Dysmenorrhea

Some prostaglandins may participate in memory and other brain functions.

Some prostaglandins sensitize nerve endings that transmit pain signals to the spinal cord and brain.

Two prostaglandins relax muscles in the lungs; another contracts them.

Two prostaglandins increase blood flow in the kidney.

Two prostaglandins protect the lining of the stomach.

Two prostaglandins contract uterine muscles; another relaxes them.

Some prostaglandins dilate small blood vessels, which leads to the redness and feeling of heat associated with inflammation.
### Biberoglu scoring system

<table>
<thead>
<tr>
<th>A. Pelvic pain</th>
<th>B. Dysmenorrhea</th>
<th>C. Dyspareunia</th>
<th>Total Pelvic Pain Score (A + B + C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None 0</td>
<td>None 0</td>
<td>None 0</td>
<td>None 0</td>
</tr>
<tr>
<td>Mild 1 = Occasional pelvic discomfort</td>
<td>Mild 1 = Some loss in work efficiency</td>
<td>Mild 1 = Tolerated discomfort</td>
<td>Mild 1 – 3</td>
</tr>
<tr>
<td>Moderate 2 = Noticeable discomfort for most of the cycle</td>
<td>Moderate 2 = In bed part of the day, occasional loss of work efficiency</td>
<td>Moderate 2 = Intercourse painful to the point of causing interdiction</td>
<td>Moderate 4 – 6</td>
</tr>
<tr>
<td>Severe 3 = Requires strong analgesics. Persist during cycle when not menstruating</td>
<td>Severe 3 = In bed one or more days incapacitation</td>
<td>Severe 3 = Avoids intercourse because of pain</td>
<td>Severe 7 – 9</td>
</tr>
</tbody>
</table>
**Biberoglu scoring system**

### D. Pelvic tenderness
<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>1 = Minimal tenderness on palpation</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 = Extensive tenderness on palpation</td>
</tr>
<tr>
<td>Severe</td>
<td>3 = Unable to palpate because of tenderness</td>
</tr>
</tbody>
</table>

### E. Induration
<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>1 = Uterus freely mobile, induration in the cul-de-sac</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 = Thickened and indurated adnexa and cul-de-sac, restricted uterine mobility</td>
</tr>
<tr>
<td>Severe</td>
<td>3 = Nodular adnexa and cul-de-sac, uterus frequently frozen</td>
</tr>
</tbody>
</table>

#### Total Physical Sign Pain Score (D + E)
<table>
<thead>
<tr>
<th>Grade</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>1 – 2</td>
</tr>
<tr>
<td>Moderate</td>
<td>3 – 4</td>
</tr>
<tr>
<td>Severe</td>
<td>5 – 6</td>
</tr>
</tbody>
</table>
### Verbal multidimensional scoring system for assessment of dysmenorrhea

<table>
<thead>
<tr>
<th>Grade</th>
<th>Working ability</th>
<th>Systemic symptoms</th>
<th>Analgesics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0: Menstruation is not painful and daily activity is unaffected</td>
<td>Unaffected</td>
<td>None</td>
<td>None required</td>
</tr>
<tr>
<td>Grade 1: Menstruation is painful but seldom inhibits normal activity; analgesics are seldom required; mild pain</td>
<td>Rarely affected</td>
<td>None</td>
<td>Rarely required</td>
</tr>
<tr>
<td>Grade 2: Daily activity is affected; analgesics required and give sufficient relief so that absence from school is unusual; moderate pain</td>
<td>Moderately affected</td>
<td>Few</td>
<td>Required</td>
</tr>
<tr>
<td>Grade 3: Activity clearly inhibited; poor effect of analgesics; vegetative symptoms (headache, fatigue, vomiting, and diarrhea); severe pain</td>
<td>Clearly inhibited</td>
<td>Apparent</td>
<td>Poor effect</td>
</tr>
</tbody>
</table>