Definitions

- Menarche – your first period
- Menses – your period
- Dysmenorrhea – painful periods
- Estrogen and progesterone – female hormones
- Androgens – male hormones (e.g. testosterone)
- Catamenial – related to periods

Introduction

- Girls menstruate. Sigh.
  - Average age of menarche: 12.5 years
- Complex interplay of hormones produced by the hypothalamus, pituitary, and ovaries
- The hormones in question do not mind their own business
  - Physical effects on the brain and body outside of the reproductive axis

Objectives

- Review the complex interrelationship between several menstrual disorders and mental health disorders
  - Dysmenorrhea
  - Premenstrual syndrome/dysphoria
  - Premenstrual exacerbation of primary psychiatric disorders
  - Polycystic ovarian syndrome
  - Chronic pain and migraines
  - Menstrual side effects of psychotropic medications
- Learn to screen for menstrual-related worsening of mental health symptoms and when to refer to an MD for further evaluation and management
Dysmenorrhea

- Dysmenorrhea (painful periods) = #1 cause of school absences in adolescent girls
- Primary vs. secondary:
  - Primary dysmenorrhea: no underlying organic disease (most common)
  - Secondary dysmenorrhea: menstrual pain is caused by an underlying organic disease

Primary dysmenorrhea:
- Usually starts 1-3 years AFTER menarche, once cycles become ovulatory
- Peaks at age 17-18 years, usually decreases in 20’s and 30’s
- Caused by prostaglandins (induced by ovulation, produced by uterine lining) which induce myometrial contractions.
- May enter circulation and cause other systemic symptoms (e.g. nausea, headache, back pain, dizziness, etc.)
- Pressure in the uterus during menses may exceed contraction pressures during labour!!

Secondary causes:
- Most common: endometriosis
- Classic triad: dysmenorrhea, dyspareunia (pain with sex), pain with defecation
- Other causes:
  - Obstructive congenital anomalies
  - STD-related (pelvic inflammatory disease or history thereof, which causes scarring)
  - Pregnancy-related
  - ovarian cysts/masses

In adolescent girls (Bahrami et al, 2017; Sahin et al, 2018):
- Strongly associated with depression, anxiety, aggression, sleep problems/insomnia, and worse quality of life
- Severity of psychiatric symptoms was worse with dysmenorrhea than with premenstrual syndrome
- Largely mediated by pain intensity

Management
- ASK if periods are painful and effect on function – far too often it is normalized!
- If dysmenorrhea began with menarche or after age 20, or if there are other associated symptoms (e.g. pain with sex, vaginal discharge, burning with urination), rule out secondary causes
- If primary:
  - NSAIDs (ibuprofen or naproxen) started PRIOR to onset of menses/pain, AND/OR
  - Contraception that inhibits ovulation (e.g. OCP, patch, ring, injectable, subdermal implant)
  - The combination works for the vast majority of girls – if it doesn’t, suspect endometriosis.
Premenstrual Syndrome And Dysphoric Disorder

BEFORE WE TALK ABOUT IT: Do Not Blame All Female Mood Symptoms On PMS!

• MOST WOMEN DO NOT HAVE PMS, although most women have at least one physical/emotional symptom prior to menses that does NOT affect function

• Romans et al, 2013:
  – 400 random women aged 18-40 followed over 6 months.
  – Only half of mood symptoms showed any menstrual cycle phase association; these links were either with the menses phase alone or the menses plus the premenstrual phase.
  – Physical health, perceived stress and social support were much stronger predictors of mood (p < 0.0001 in each case) than menstrual cycle phase.

Premenstrual Syndrome (PMS) Criteria (ACOG, 2014)

• Symptoms: At least ONE physical or emotional symptom (Hartlage et al, 2012)
  – Physical: fatigue (most common), bloating, headache, breast tenderness, GI upset, back pain, hot flashes, dizziness
  – Emotional: mood swings (most common), irritability, anxiety/tension, sad or depressed mood, increased appetite/food cravings, sensitivity to rejection, and diminished interest in activities

• Timing:
  – Occurs 5 days prior to onset menses and resolves within a few days of onset of menses
  – Peak: 4 days before to 2 days after onset (Hartlage et al, 2012)
  – Occurs over at least 3 consecutive menstrual cycles
  – THERE IS A SYMPTOM-FREE INTERVAL

• Exclusions:
  – NOT just premenstrual exacerbation of MDD/anxiety/personality disorder, etc
  – NOT caused by concurrent substance abuse or medical condition

• Severity: has an effect on function (school, work, relationships)
• Verified over at least 2 cycles

Pathophysiology Of Premenstrual Mood Changes

• Hormonal contributors (Wardlaw et al, 1982; Majewska et al, 1986; Bethea, 1994)
  – Normal levels of estrogen and progesterone, but abnormal response to normal hormonal changes
  – Cyclic fluctuations in circulating estrogen and progesterone cause marked changes in the opioid, GABA, and serotonin systems – more exaggerated in some women than others

• In perimenstrual phase: higher experiences of persecution, negative self esteem, anxiety, and depression (Brock et al, 2016)
  – Increased paranoid perceptions  ➔ increased interpersonal sensitivity and impact on relationships
Premenstrual Dysphoric Disorder (PMDD)

- Newly included in DSM5 (APA, 2013)
- At least 5 symptoms, at least ONE of which is a severe affective symptom (markedly severe mood swings, irritability/anger; depressed mood, anxiety, or anhedonia) for most menstrual cycles over the last year
- Timing: same as PMS
- Severity: MARKED effect on FUNCTION
- Exclusions: same as PMS
- CONFIRMED by prospective daily symptom ratings over at least 2 cycles

PMS/PMDD

- Can start anytime after menarche but usually established by your 20’s
- Prevalence in adolescents of moderate to severe PMS is at least 20% (Rapkin and Mikacich, 2008)
- Independent predictors of PMDD symptoms (Osman et al, 2017):
  - higher education, major life stressor, personal use of psychotropic medications, personal/family hx of psychological problems, and painful menses

Treatment Of PMS/PMDD

- In general:
  - There is a very high placebo response rate for treatments of PMS/PMDD
  - Not a lot of treatments show effects superior to placebo!
- Mild symptoms: lifestyle modification may be enough
  - Exercise
  - Sleep hygiene
  - Balanced nutrition
  - Relaxation techniques and stress reduction
  - Getting sufficient dietary calcium
  - Natural remedies:
    - Black cohosh, chasteberry may help
    - Integrative medicine: maybe acupuncture

- Moderate/severe symptoms:
  - FIRST LINE TREATMENT is SSRI medication (clearly superior to placebo)
  - Works in 60-70% of women with PMDD
  - More effective for emotional symptoms than somatic symptoms
  - Works with FIRST CYCLE unlike other mood/anxiety disorders
  - Options: continuous, luteal phase therapy (starting day 14, stop at menses), or symptom-onset therapy (just take on symptomatic days)
    - ALL are effective
    - Choose based on pattern of symptoms, adherence, comorbid anxiety/depression, etc

- Second-line treatment: Combined oral contraceptive pills (OCPs)
  - Probably more effective for physical symptoms than emotional symptoms (Yonkers et al, 2017; Ekenros et al, 2019) but also more likely to worsen emotional symptoms
  - Works by inhibiting ovulation
  - Use of a 4-day hormone-free interval seems to be more effective than 7 days
  - Can also be combined with SSRI

- Less well studied:
  - Medroxyprogesterone acetate (injectable birth control) also inhibits ovulation, but may also worsen some symptoms
  - Gonadotropin-releasing hormone (GnRH) agonists
    - Suppressed hormonal levels altogether at the level of the hypothalamus
    - Usually requires add-back hormonal therapy
  - If you’re REALLY desperate: bilateral oophorectomy and hysterectomy (removal of ovaries/uterus)
    - LAST RESORT
Premenstrual Exacerbation Of Other Psychiatric Disorders

- Premenstrual worsening of symptoms associated with a primary psychiatric disorder
- An interesting study: Targum et al, 1991
  - 51 women admitted with psychiatric emergencies
  - 47% were in the perimenstrual phase in contrast to 22% of staff controls
  - 33.3% of admissions occurred within 4 days of the onset of menstruation
  - Included depression, bipolar disorder, and psychotic disorders
  - No significant phase differences found between specific diagnoses or suicidal vs nonsuicidal

- E.g. Among premenopausal women with MDD (Kornstein et al, 2005): 64% reported premenstrual exacerbation of depression—these women were:
  - More likely to have had longer duration of current MDD episode
  - More general medical comorbidity
  - More somatic complaints and psychomotor retardation with MDD

- E.g. Among women with bipolar disorder (Teatero et al, 2014): Menstrual cycle-related mood changes reported by 64-68% of women with BD in retrospective studies, and displayed by 44-65% of women in prospective studies
  - Mood changes could be depressive, manic, or hypomanic

- Other conditions which may be more symptomatic premenstrually: generalized anxiety disorder, schizophrenia, borderline personality disorder (Einsteins-Moul et al, 2010; Sooman, 2012; Halis et al, 2014)

- This is NOT PMS/PMDD
- But, probably similar underlying effects of cyclic hormonal changes on neurotransmitters (opioid, GABA, serotonin)
- The UNDERLYING primary psychiatric disorder requires treatment
- BUT: consideration of hormonal contraception may be a helpful adjunct

Polycystic Ovarian Syndrome (PCOS)

- Affects up to 10% of girls and women – 1 in 10
- Complex endocrine condition – pathophysiology not totally clear, but appears related to insulin resistance and relative hyperinsulinemia
  - Results in excessive androgen production and impaired ovulation
- Classic symptoms: irregular periods, symptoms of hyperandrogenism (body/facial hair, acne, body odor), infertility, obesity (in about 50%)
- Risks if not treated:
  - Development of type II diabetes mellitus
  - Uterine cancer
PCOS And Mental Health

- Adolescents and adults with PCOS are significantly more likely to experience depression and anxiety (Glintborg et al., 2015; Dokras, 2012; Cinar et al., 2011; Weiner et al., 2004)
  - One study (Cinar et al.) showed an 8-fold risk of depression in PCOS vs controls
  - There may be an association between obesity and metabolic abnormalities in PCOS with depression/anxiety, but this is poorly understood (Dokras et al., 2012; Cinar et al., 2011)
  - There may be an association between elevated androgens in PCOS and depression (Weiner et al., 2004)
  - Body image component?

PCOS

- Mental health providers may be the first to detect possible PCOS
  - Should refer to MD for evaluation and treatment
- Women with PCOS should be particularly screened

Chronic Pain and Menstrual Exacerbation

- Premenopausal women with fibromyalgia (Pamuk and Cakir, 2005):
  - 45% reported higher pain severity and 57.5% reported higher fatigue severity during menses
  - Those who reported worse symptoms during menses were also the ones with worse sleep disturbance, worse somatization symptoms, and more tender points
- Unclear whether contraception could help - but it might be worth a shot

Catamenial Disorders

- “Catamenial” – physical disorders that are worse with menses
  - Migraines
  - Epilepsy
- Can be incredibly debilitating
- Inhibition of ovulation with contraception can be life-changing for women with catamenial physical disorders
Effects Of Psychotropic Medications On Menses

- Lithium → thyroid dysfunction → menstrual irregularity; other metabolic effects
- Atypical antipsychotics → hyperprolactinemia → menstrual irregularity, galactorrhea
- Atypical antipsychotics → weight gain, insulin resistance → menstrual irregularity (similar to PCOS)
- Valproic acid → PCOS-like symptoms (hirsutism, weight gain, acne)

Summary:

- Ask patients/clients if they have dysmenorrhea, explore impact on function, and REFER to MD for evaluation/treatment.
- Ask patients/clients about premenstrual physical and emotional symptoms
  - Suggest lifestyle modification for mild cases
  - REFER to MD for moderate/severe cases for consideration of SSRIs and/or contraception
- Ask patients with primary psychiatric disorders about premenstrual exacerbation of symptoms
  - Suggest referral to MD for adjunctive contraceptive management

Summary:

- PCOS
  - Recognize possible symptoms and refer to MD for evaluation
    - Screen girls with known PCOS for anxiety, depression, and body image problems
  - Patients with debilitating chronic pain, especially migraines
    - Ask about worsening of symptoms with menses and suggest referral to MD for contraceptive management
  - Be aware that menstrual irregularity can be a side of psychotropic medications - and may indicate a more serious underlying endocrine disturbance

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