Riding The Crimson Wave: Menstrual Disorders And Mental Health In Adolescents

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Disclosures

- No conflicts of interest or financial relationships to disclose

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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

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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

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Introduction

- Result:
  - Menses can cause significant primary physical and psychiatric symptoms
  - Menses can trigger secondary worsening of other primary medical and psychiatric conditions
- Just one example of the importance of the bidirectional relationship between physical and mental health and resultant effects on function

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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

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Dysmenorrhea

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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

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Dysmenorrhea

- 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!!

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Dysmenorrhea

- 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/mass

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Dysmenorrhea

- 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

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Dysmenorrhea

- 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.

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Premenstrual Syndrome And Dysphoric Disorder

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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

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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

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Premenstrual Syndrome (PMS) Criteria (ACOG, 2014)

- 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

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Premenstrual Syndrome (PMS) Criteria (ACOG, 2014)

- 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

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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

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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

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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

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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:
    - Herbal remedies: chasteberry is the only one that might work
    - Integrative medicine: maybe acupuncture

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Treatment Of PMS/PMDD

- 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

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Treatment Of PMS/PMDD

- Moderate/severe symptoms
  - 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 does modestly improve 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

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Treatment Of PMS/PMDD

- Less well studied:
  - Medroxyprogesterone acetate (injectable birth control) also inhibits ovulation, but may also worsen some symptoms
  - Etonogestrel acetate (subdermal implant) also inhibits ovulation
- If you're desperate: GnRH agonists
  - Suppresses hormonal axis 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
  - Childbearing is complete
  - GnRH agonists have been effective for at least 6 months

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Premenstrual Exacerbation Of Other Psychiatric Disorders

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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 their the perimenstrual phase in contrast to 22% of staff controls
  - 33.3% of admissions occurred within 4 days of the onset of menses
  - Included depression, bipolar disorder, and psychotic disorders
  - No significant phase differences found between specific diagnoses or suicidal vs nonsuicidal

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Premenstrual Exacerbation Of Other Psychiatric Disorders

- 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 (Eisenlohr-Moul et al, 2018; Seeman, 2012; Hsiao et al, 2004)

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Premenstrual Exacerbation Of Other Psychiatric Disorders

- 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

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Polycystic Ovarian Syndrome

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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

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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 at 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?

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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

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Chronic Pain And Catamenial Disorders

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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

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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

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Psychotropic Medications And Menstrual Irregularity

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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)

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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 SSRI and/or contraception
- Ask patients with primary psychiatric disorders about premenstrual exacerbation of symptoms
  - Suggest referral to MD for adjunctive contraceptive management

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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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Thank You!

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