NATIONAL CURRICULUM IN REPRODUCTIVE PSYCHIATRY

Overview

Progressive Case Conference: Across the Reproductive Life Cycle

Facilitator's Guide

Contributors

Lucy Hutner, MD
Nicole Leistikow, MD
Jovana Martinovic, MD
Lauren M. Osborne, MD

Pre-Session Assignment

Before attending this session, please review the following:

1) The reproductive life cycle self-study power point
2) The physiology of pregnancy self-study power point [link to self-study materials here]
3) Pre-reading:

Sramek J, Murphy M, Cutler N. Sex differences in the psychopharmacological treatment of depression. Dialogues in Clinical Neuroscience 2016 18 (4) 447-457.

Dutton and Rymer, "Physiology of the menstrual cycle and changes in perimenopause," in *Managing the Menopause: 21st Century Solution*, Cambridge University Press, 2015.

Soares, C. Depression and menopause: current knowledge and clinical recommendations for a critical window. Psych Clin North Amer 40 (2017) 239-25

Joffe H, Soares CN, Cohen LS. Assessment and treatment of hot flushes and menopausal mood disturbance; Psychiatr. Clin. North Am., 26 (2003), pp. 563-580.

Reddy DS. Clinical pharmacokinetic interactions between antiepileptic drugs and hormonal contraceptives. Expert Rev Clin Pharmacol. 2010 Mar 1;3(2):183-192.

Christensen J, Petrenaite V, Atterman J, Sidenius P, Ohman I, Tomson T, Sabers A. Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, placebo-controlled trial. Epilepsia. 2007 Mar;48(3):484-9.

Overview

This case conference will follow a woman from early adult life (normal menstrual cycle) through conversations about contraception, premenstrual symptoms, and perimenopause. Pregnancy will not be covered as it is the focus of other sections of this curriculum. It is assumed that trainees will have reviewed the self-study materials for the reproductive life cycle prior to participating in this case conference.

Session Outline

- Discussion of self-study materials (10 min)
- Apply knowledge to a clinical case (40 minutes)
- Wrap-up/review (10 minutes)

Learning Objectives

At the completion of this session and accompanying self-study materials, participants will be able to:

1. Describe the stages of the menstrual cycle and their clinical impact

2. Describe the prevalence and symptoms of premenstrual disorders, including premenstrual syndrome, premenstrual dysphoric disorder (PMDD), and premenstrual exacerbation of another mood disorder
3. Understand treatment options for PMDD and premenstrual exacerbation of mood disorders
4. Understand how to distinguish among symptoms in premenopause, perimenopause, and post-menopause and be able to counsel patients on the risk of psychiatric illness during these times
5. Discuss treatment options for both depression and physical symptoms of perimenopause

Clinical Case

Part 1: Early adult life, normal menstrual cycle

Felicity C., a 26-year-old G0P0 Caucasian single woman who works as an event planner, presents for routine care to her psychiatrist. She is currently taking escitalopram 10 mg PO daily, which has been effective for a single episode of moderate depression. She wishes to know whether her psychiatric medication will make a difference in the type of contraception she chooses.

Facilitator pauses for discussion:

1. Do we need to worry about interactions between Felicity's psychiatric medication and contraception? If not, in what circumstances would we worry?
   Elicit the following:
   - There are no interactions to be concerned about with SSRIs and hormonal contraception. Some psychiatric medications DO have interactions with hormonal contraception. They include:

Lamotrigine:

- Elicit interaction between lamotrigine and estrogen-containing contraceptives.
- Elicit that estrogen decreases serum levels of lamotrigine: Lamotrigine is metabolized primarily by glucorinidation by UGT 1A4 and is renally excreted. Ethinyl estradiol is also glucorinidated by UGT 1A4 and estrogens are known inducers of UGTs. The interaction thus leads to increased renal excretion of lamotrigine. Note that this is NOT a cytochrome P450 interaction!
- Elicit theoretical differences in that interaction between monophasic or triphasic and during placebo week – monophasic have steady level of estrogen all month, so would expect symptoms stable across three weeks and different in placebo week; triphasic are up and down, so would expect fluctuation in symptoms. Lamotrigine half-life is about 37 hours, so these fluctuations could make a difference in symptoms – *though evidence to support this point is scant at best.*
- Elicit benefits of continuous contraception in those on lamotrigine who use OCPs (no placebo week, so can adjust dose of lamotrigine and keep it stable throughout cycle)

Carbamazepine:

- Carbamazepine is a CYP-3A4 inducer (as are phenytoin, barbiturates, primidone, topiramate, and oxcarbazepine) that induces hepatic metabolism (P450). This activity on liver metabolism can decrease hormonal contraceptive levels and efficacy.
- Etonorgestrel implant has reduced efficacy when women are also taking carbamazepine. If the patient really wants to use Etonorgestrel Implant she should also use a barrier contraception or other non-hormonal contraception. The etonorgesterol implant has the highest efficacy of any LARC, and 0.05% failure rate – so this is the best method to prevent pregnancy.
- Depo-Provera does not have effectiveness reduced by hepatic enzyme inducers. Perhaps this is due to the dosage and administration (intramuscular).
-

Part 2: Premenstrual symptoms

Felicity's treatment with escitalopram is successful, and she tapers off the medication after one year with no withdrawal effects and no resumption of her mood symptoms. Two years later, however, she returns to her psychiatrist with a chief complaint of "there's something wrong with my hormones." She reports no acute gynecologic issues or sexually transmitted infections, and no medical problems beyond obesity (BMI 31) and mild intermittent asthma that she controls with an albuterol inhaler. She underwent menarche at age 12, the same age as her mother and older sisters, one of whom has fibroids and menorrhagia. Her periods were irregular and scant for the first two years, but by age 14 she was experiencing heavy and prolonged bleeding, accompanied by severe pain and mood changes. Her mother took her to the pediatrician, who recommended oral contraceptives, which Felicity used for the next 12 years; her pain and mood symptoms improved with the oral contraceptive, and have not been interfering with her life (except during her one prior episode of depression two years ago).

Recently, however, Felicity's middle sister was diagnosed with Factor V Leiden, and Felicity's gynecologist mentioned that the blood clotting disorders were relative contraindications for hormonal contraception. Felicity stopped her oral contraceptive, and within two months she was again experiencing heavy bleeding and severe cramping during her menses, along with mood changes, bloating, and breast tenderness in the two weeks prior to menses. She wants to know what she can do about these symptoms.

Facilitator pauses for discussion:

2. What is the differential diagnosis for Felicity's symptoms at this point?

Elicit the following:

- PMS
- PMDD
- PM exacerbation of another disorder
- Gynecologic condition such as fibroids
- We don't have enough information about her symptoms right now to be able to distinguish among the three premenstrual syndromes, nor to rule out conditions such as fibroids that may explain her heavy bleeding.

3. What risk factors for premenstrual disorders are already mentioned in the case presentation? What additional risk factors are there that may or may not be present for this patient?

Elicit the following:

Already mentioned:

- White
- Obese

Still unknown:

- Cigarette smoking
- History of early trauma/sexual abuse
- Familiality

Case continued

On subsequent conversation, Felicity reports that she is lashing out at other people during the week prior to menses; she has gotten into several fights with her boyfriend, and was nearly fired for insubordination and has been mandated to go to anger management classes at work. At times she also reports suicidal thoughts in the week prior to menses, and has been thinking about two full bottles of ibuprofen in her medicine chest as a means to overdose; she has gone as far as taking the bottles out of the cabinet but has not opened them. She reports that her symptoms begin about 10 days prior to menses and clear up entirely on the second day of bleeding.

Facilitator pauses for discussion.

4. What diagnosis do you most strongly suspect now?

Elicit the following:

- PMDD
- Briefly remind trainees of DSM-5 Criteria, which they reviewed in self-study:

A. In most menstrual cycles, following symptoms must be present in final week before onset of menses, start to *improve* within few days after onset of menses, and become *minimal or* absent in week postmenses– at least 1 symptom must be either (1), (2), (3), or (4) and individual must experience at least 5 total symptoms:
1. Marked affective lability (eg, mood swings; feeling suddenly sad or tearful or increased sensitivity to rejection)
2. Marked irritability or anger or increased interpersonal conflicts
3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts
4. Marked anxiety, tension, feelings of being "keyed up," or "on edge"
5. Decreased interest in usual activities (eg, work, school, friends, hobbies)
6. Subjective difficulty in concentration
7. Lethargy, easy fatigability, or marked lack of energy
8. Marked change in appetite, overeating, or specific food cravings
9. Hypersomnia or insomnia
10. A sense of being overwhelmed or out of control
11. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, sensation of "bloating," weight gain

B. Symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships

C. Disturbance is not merely exacerbation of symptoms of another disorder

D. Criterion A should be confirmed by prospective daily ratings during at least 2 symptomatic cycles (diagnosis may be made provisionally prior to this confirmation)

E. Symptoms are not due to direct physiological effects of substance (eg, drug of abuse, medication or other treatment) or another medical condition (eg, hyperthyroidism)

5. What do you need to do now to confirm this diagnosis?
Elicit the following:
- Obtain 2 months' worth of prospective mood ratings, using a tool such as Daily Record of Severity of Symptoms or a mood tracker app such as Flo

6. How do we know this is not PMS?
Elicit the following:

- Women who have predominantly physical symptoms, or whose distress is below the threshold required for PMDD, have PMS.

7. How do we know this is not premenstrual exacerbation of an underlying mood disorder?
Elicit the following:

We don't yet! Felicity does have a history of depression, so this may be depression with premenstrual exacerbation. Only prospective ratings will tell us for sure that this is PMDD.

Case continued.

Felicity's physician advises her to fill out the Daily Record of Severity of symptoms for the next two cycles, and after that gives her a diagnosis of PMDD. Felicity asks what she can take to feel better.

8. How do we treat PMDD?

Elicit the following:

- Nonpharmacological approaches can be helpful. These include exercise, diet (a complex carbohydrate diet in the luteal phase was helpful in one randomized trial), and psychotherapy, particularly CBT.
- SSRIs are first-line treatment, and there is strong evidence of their efficacy
- Can be dosed continuously, or with luteal phase or symptom onset dosing. Some evidence indicates that continuous dosing may be slightly more effective, but there isn't much evidence about that yet.
- Combined oral contraceptives are commonly used, but evidence is actually sparse – and they have a number of downsides (higher risk than SSRIs of blood clots, stroke, etc.). The best evidence concerns those that use the novel progestin drosperinone, so for women who desire contraception and have no contraindications, this may be a reasonable alternative to an SSRI.
- Data for other hormonal treatments, i.e., estrogen and progesterone, is inadequate.
- For severe cases, GnRH agonists can be used to stop ovulation, but this is very much a third-line treatment.
- Hysterectomy and oophorectomy could also be used for refractory cases, but these invasive procedures should be recommended with caution, and only after first trying GnRH agonists to see if the hypoestrogenic state is a) tolerable and b) helpful
- Complementary medicines are frequently used, but evidence and effect sizes at this point are low; chasteberry is increasingly studied and may accumulate sufficient evidence in time. There is some evidence for vitamin B6 (100 mg) and calcium (1000 mg).

9. Does it make sense to use SSRIs in luteal phase dosing? Don't they take 6-8 weeks to work?
Elicit the following:

- Not in PMDD! They work right away. Clearly the mechanism is different, but we are not quite sure why. They may act on allopregnanolone.

10. How does treatment differ if the patient is found to have premenstrual exacerbation of an underlying disorder?
Elicit the following:

- Treatment for the underlying mood disorder should be maximized before beginning any specific premenstrual treatment; for many, the premenstrual exacerbation will disappear when the mood disorder is treated. If it does not, extra SSRI can be added in the luteal phase.

Part 3. Perimenopause

Felicity is successfully treated for her PMDD and has no further episodes of depression across her reproductive years. At age 47, she presents again with 8 weeks of difficulty sleeping, low energy, increased anxiety about her family and work, higher irritability, feeling more "moody," having trouble getting tasks done at home and at work, and feeling that she is failing at her many obligations. She told her OB/GYN during a routine pap smear that sometimes she has days where she wonders if she can go on with life anymore and was tearful, prompting this referral.

Facilitator pauses for discussion:

11. Which questions can you ask to determine where she is in the transition to menopause and why is this relevant?
Elicit the following:

- It helps me understand what might be going on to know whether hormonal changes could be contributing. Are you still having periods, and if so, how frequent have they been in the last 6 months?

- Perimenopause is a time of increased risk of depression, mainly for women with a prior history of depression, with some studies also showing increased risk for those without a prior history.[1]

- Premenopausal = regular menstrual cycles during the last 3 months;
- perimenopausal = 3–11 months of irregular menses or amenorrhea
- postmenopausal=12 or more months of amenorrhea[2,3]

12. If you determine that Felicity is in perimenopause, what are some of the physical symptoms/changes that may overlap with and complicate mood and anxiety disorders?
Elicit the following:

- Hot flashes affecting sleep
- Weight gain
- Sexual dysfunction or decreased sexual drive
- Muscle and joint aches
- Urinary problems
- Cognitive changes[4]

13. What are some rating scales you could use if you wanted to track or measure some of these symptoms?
Elicit the following:

- Menopause Rating Scale
- Greene Climacteric Scale
- Hot Flash daily Interference Scale
- Pittsburgh Sleep Quality Index
- Montreal Cognitive Assessment

Case continued.

On further discussion, Felicity describes forgetfulness, physical aches and pains, vaginal dryness, irritability, worry, weight gain, sleep latency, and frequent nocturnal awakenings. Her provider asks further questions to determine what else is going on in her life and what other physical symptoms she may be having.

14. What are some social stressors common to this age group that you might screen for?
Elicit the following:

- Caregiving for aging parents
- Relationships with adolescent or adult children
- Job demands
- Stress with partners
- Reduced time for self
- Changes in exercise, eating, socialization

---

[1] Maki, Pauline M., et al. "Guidelines for the Evaluation and Treatment of Perimenopausal Depression: Summary and Recommendations." *Journal of Women's Health*, Sept. 2018.
[2] Carpenter, Janet S. "The Hot Flash Related Daily Interference Scale." *Journal of Pain and Symptom Management*, vol. 22, no. 6, Dec. 2001, pp. 979–89.
[3] Bromberger JT, Matthews KA, Schott LL, et al. Depressive symptoms during the menopausal transition: the Study of Women's Health Across the Nation (SWAN). J Affect Disord 2007;103:267–272.
[4] Greendale, G. A., Derby, C. A., & Maki, P. M. (2011). "Perimenopause and cognition." *Obstetrics and gynecology clinics of North America*, *38*(3), 519-35.

15. What are important medical issues to rule out, investigate, or consider in this population, basic labs to get?
Elicit the following:

- Thyroid problems
- Diabetes
- High blood pressure
- Untreated cardiovascular risk factors such as high blood pressure or smoking
- If having hot flashes, other possible causes of these symptoms such as infection, carcinoid, or malignancies.
- Inquire whether patients are getting routine mammograms and colonoscopies and encourage them to see their primary care doctor if not.
- CBC, CMP, and TSH/FT4 are a good place to start.

Case continued.
Felicity reports further difficulty "coping with everyday stresses," and acknowledges that she has increased her consumption of wine from one glass 3-4 times weekly to two glasses every night. She mentions feeling guilty and exhausted nearly all the time.

Facilitator pauses for discussion

16. Based on what you've heard so far, what diagnoses are on your differential?
Elicit the following:
Major depression, recurrent, moderate to severe with premenstrual exacerbation
Adjustment disorder with perimenopausal symptoms
Substance induced mood disorder
Normal symptoms of perimenopause

17. What are some pharmacologic treatment options you could recommend? What published summaries are helpful for understanding the evidence for these recommendations?
Elicit the following:
Antidepressants - typical first choices with some evidence for also treating vasomotor symptoms might be venlafaxine, desvenlafaxine, fluoxetine, paroxetine, citalopram, escitalopram.

See Joffe 2003 pre-reading.

Hormone Therapy
18. What are the contraindications for Hormone Therapy?
Elicit the following:
Contraindications to Oral Contraceptive/Hormone Therapy use—include:

- a history of myocardial infarction (MI)
- thromboembolism
- stroke
- breast cancer
- serious liver disease
- smoking cigarettes
- being in menopause (age 55 typically a proxy).

19. Which types of psychotherapy would likely to be helpful for this patient, and which topics might she benefit from exploring?
Elicit the following:
Boundary setting, Interpersonal Therapy (IPT), Cognitive Behavioral Therapy, family therapy, focus on asserting and communicating needs