WOMEN’S HEALTH – A NATURAL APPROACH TO HORMONE CARE PART 1
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DR. SARAH DALHOUMI, MD
SCRIPPS CENTER FOR INTEGRATIVE MEDICINE
Disclosure

- Dr. Sarah Dalhoumi has no financial disclosures that would contribute to a conflict of interest
OBJECTIVES

- Understand the role of sex hormones in the female cycle
- Review the pathophysiology of disruptions within this cycle
- Explore the symptoms of PMS and PMDD and treatment options
- Learn how to support a patient facing infertility and explore their options
- Discuss how natural supplements and CAM can contribute to improvement of these medical conditions.
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<th>Hormone</th>
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<td>FSH</td>
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<td>• Inhibits LH and FSH (luteal phase)</td>
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How Hormones Are Made in Your Body

Cholesterol → Pregnenolone → Progesterone → 17, OH Progesterone → Androstenedione → Testosterone → Estradiol (E2) → Estrone (E1)

11 DOC (Deoxy-corticosterone) → Corticosterone → 18 Hydroxy-corticosterone → Aldosterone (Mineralocorticoid)

DHEA → 17, OH Pregnenolone → 11 Desoxycortisol → Cortisol (Glucocorticoid)
Monthly Cycle

![Graph showing cycle with peaks for Estrogen and Progesterone over 28 days with period begins and ovulation stages marked]
The Menstrual Cycle

Pituitary hormones:
Just before ovulation, your hypothalamus and pituitary gland release FSH (follicle stimulating hormone) and LH (luteinizing hormone) to trigger ovulation.

Uterus lining:
The uterus thickens to support a pregnancy and then sheds if there is no egg to support.

Egg development:
As our ovaries ripen follicles (or eggs), estrogen levels begin to rise.

Ovarian hormones:
Estrogen levels rise until ovulation occurs. After ovulation, estrogen levels gradually decline and progesterone levels rise. Many PMS symptoms can arise due to a higher than normal estrogen to progesterone ratio.

Phases of the moon:
It is believed that before the advent of artificial light, prescription drugs, and technology, women's periods more closely corresponded with the moon.
Premenstrual Syndrome (PMS)
PMS
Premenstrual syndrome (PMS) is a common disorder, and many affected women will end up in a gynaecologist’s office. Even a cursory review of the subject will reveal a lack of consensus concerning the aetiology of PMS and its causes. However, there do appear to be at least three components to the aetiology of PMS:

- a brain component
- an ovulatory menstrual cycle
- psychosocial factors and other factors

Women who suffer from severe PMS commonly date their symptoms from the mid-forties, and may be seen by a mental health professional who may lack knowledge of the problem. Even worse, they might be accused of purely expressing their personality, or being neurotic. (They are not.)

Confirming a diagnosis

The most popular definition is that of the American College of Obstetricians and Gynaecologists (ACOG) (see Table 1).

The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (1994) is used for the diagnosis of premenstrual dysphoric disorder (PMDD). This identifies women with more severe emotional symptoms.
Know Your Symptoms

**PMDD**
Premenstrual dysphoric disorder

**PMS**
Premenstrual syndrome

Bloating / Gaseous
- Low energy
- Feeling anxious or nervous

Anger / Irritability
- Sadness
- Crying

Strong food cravings

Problems
- Paying attention
- Concentrating
- Fatigue and trouble
- Sleeping

Tender breasts

Clumsiness
- Constipation
- Diarrhea

Food cravings
- Headaches
- Less tolerance for noise & light

Women experience these truly disruptive symptoms for at least half of their cycles throughout the year. Symptoms start after ovulation & end when period starts. Symptoms only occur under hormonal states (not continual depression)

Many shared symptoms with PMDD though not as severe as PMDD. Symptoms start after ovulation & end when period starts.
DIAGNOSTIC CRITERIA

Table 1
Diagnostic Criteria for PMS

A. PMS can be diagnosed if the patient reports at least one of the following affective and somatic symptoms during the five days before menses in each of the three prior menstrual cycles:

Affective Symptoms
- Depression
- Angry outbursts
- Irritability
- Anxiety
- Confusion
- Social withdrawal

Somatic Symptoms
- Breast tenderness
- Abdominal bloating
- Headache
- Swelling of extremities

B. These symptoms are relieved within 4 days of the onset of menses without recurrence until at least cycle day 13

C. The symptoms are present in the absence of any pharmacologic therapy, hormone ingestion, or drug or alcohol use

D. The symptoms occur reproducibly during two cycles of prospective recording

E. The patient suffers from identifiable dysfunction in social or economic performance

PMS = premenstrual syndrome.


Table 2
Research criteria for PMDD (DSM-IV-TR)*

A. Symptoms must occur during the week before menses, improve several days after the onset of menses and remit for up to 7 days.

Five or more of the following symptoms must be present, and at least one must be (1), (2), (3), or (4):

1. Depressed mood or hopelessness
2. Anxiety or tension
3. Affective lability
4. Irritability or anger
5. Decreased interest in usual activities
6. Concentration difficulties
7. Marked lack of energy
8. Marked change in appetite, overeating, or food cravings
9. Hypersomnia or insomnia
10. Feeling overwhelmed or out of control
11. Other physical symptoms i.e., breast tenderness, bloating

B. Symptoms must interfere with work, school, usual social activities or relationships.

C. Symptoms are not merely an exacerbation of another disorder.

D. Criteria A, B, and C must be confirmed by prospective daily ratings for at least two consecutive symptomatic cycles.

*Summarized.
Sorry if I seem agitated—I just laid an egg, and now my body is violently ripping down the walls of my uterus, which it does 12 times a year.
Women complain about premenstrual syndrome, but I think of it as the only time of the month that I can be myself.

(Roseanne Barr)
PMS

- ↓ Estrogen
- ↓ Progesterone
- ↑ Aldosterone
- ↑ Prolactin
- ↓ Dopamine
- ↓ Endorphins
- Serotonin
- GABA –alpha receptors
- Prostaglandins
- Fluctuations lead to increase irritability, increase fluid retention, depression, sadness, headaches, and breast tenderness
CALCIUM AND PMS

- Calcium has a long history in treatment of PMS and menstrual disorders dating back to the 1930’s.
- Multiple clinical trials have shown Calcium supplementation to reduce total PMS related symptoms compared to placebo.
- One study out of Columbia found 48% reduction after calcium supplementation for three consecutive menstrual cycles.
- Recommend 1200 mg/day.

Thys-Jacobs s et al 1998
CHASTE TREE FRUIT
(VITEX AGNUS CASTUS)

- Sometimes referred to as the “women’s herb”
- Native to the Mediterranean Basin

- Also referred to as: Monk’s pepper, Abraham’s balm, and Wild pepper
- In Germany approved for PMS and mastalgia
- Dose: 20-30mg/day Chasteberry extract
CHASTE TREE FRUIT
(VITEX AGNUS CASTUS)

- Mechanism of action not fully understood
- Dopamnergic effects – compounds in chaste tree berry bind Dopamine (D2) receptors in the hypothalamus and anterior pituitary, thus inhibiting the release of prolactin
- At low levels, via competitive binding, causes a slight increase in prolactin levels
- At higher levels, binding activity is sufficient to reduce release of prolactin
- Decreases in prolactin influence FSH and estrogen levels

Jang et al, BMC Complementary and Alternative Medicine 2014, 1
CHASTE TREE FRUIT
(VITEX AGNUS CASTUS)

- In 4 RCT’s comparing Vitex Agnus Castus vs control showed:
  - VAC superior to placebo over 3 cycles for total PMS symptoms measured on the PMTS and PMSD scales
  - In all studies on VAC, psychological and physical symptoms showed more than 50% improvement over control groups
  - One study with Fluoxetine as a comparative drug, there was no significant difference between the two groups, except in the Fluoxetine group there were two adverse events of sexual dysfunction
  - Doses ranged from 20-40mg daily

Jang et al, BMC Complementary and Alternative Medicine 2014, 14:11
Approximately 40% of women report PMS
In 2-10% of cases it is severe enough to affect lifestyle and job
RCT evaluating the effect of omega-3 fatty acids on treatment of PMS
Study compared 2g omega-3 to placebo in 124 eligible women
Severity and duration of each of the symptoms were compared in both groups 1.5 and 3 months after beginning treatment
After 45 days the mean severity of depression ($P=0.03$), anxiety ($P=0.2$), lack of concentration ($P=0.03$), and bloating ($P=0.02$) were all significantly lower than control group
After 90 days from starting treatment the mean severity of depression ($P=0.007$), anxiety ($P=0.004$), lack of concentration ($P=0.009$), bloating ($P=0.004$), nervousness ($P=0.01$), and duration of depression ($P=0.01$), headache ($P=0.04$), and breast tenderness ($P=0.02$) were all lower in the case group

Conclusion: Omega-3 fatty acids may reduce the psychiatric symptoms of PMS including depression, nervousness, anxiety, and lack of concentration and may also reduce the somatic symptoms of PMS including bloating, headache, and breast tenderness. Also, these effects increased by longer duration of treatment.

Ginger and PMS Symptoms

- Randomized double-blinded placebo-controlled study looking at the effect of treatment with ginger on the severity of PMS symptoms

- 70 female students (18-35 years old) were randomized to intervention (ginger 250mg/BID) and control (placebo capsule) groups given 7 days before menstruation to 3 days after for 3 cycles

- Recorded severity of symptoms by daily record scale questionnaire

*ISRN Obstetrics and Gynecology. 2014 Article ID 792708*
Results: Before intervention, there were no significant differences between the mean scores of PMS symptoms between the two groups.

After 1, 2, and 3 months of treatment, there were significant differences regarding the total score of PMS, severity of mood, and physical and behavioral symptoms between the two groups (P<0.0001) after intervention.

Conclusion: Ginger can be an appropriate treatment in reducing symptoms of premenstrual syndrome.

Mechanism of action: Ginger prevents the production of prostaglandins through the inhibition of the metabolism of cyclooxygenase and lipoxygenase.
Clinical randomized double blind trial comparing the effects of Chamomile Extract and Mefenamic acid (MA) on the intensity of PMS symptoms

- 90 student participants

- Participants were divided into two groups, each receiving either Chamomile capsule 100mg or MA 250 mg TID.

- Participants filled out daily forms about intensity of PMS for two consecutive months.

- Intensity reduction of emotional symptoms was significantly higher among Chamomile Extract users than the MA users after two cycles of intervention (P > 0.05)

- Intensity reduction of physical symptoms was not significantly different between groups

- Conclusion: Consumption of chamomile seems to be more effective than MA in relieving the intensity of PMS associated symptomatic psychological pains

PMDD affects approximately 7% of reproductive age women. Results in impaired relationships, diminished overall quality of life, and disability-adjusted life years lost on par with other major psychiatric disorders. Pharmacological treatment is inadequate in approximately 50% of women with PMDD. 6 women completed double-blind crossover study of chromium (chromium polynicotinate) 400mcg/day + placebo versus chromium + sertraline. Treatments were administered from mid-cycle to onset of menses in 1 month intervals. Symptom rating were obtained by self report using daily symptom checklists, clinical assessment, Hamilton Psychiatric Rating Scale for Depression (HAM-D) and the Clinical Global Impressions (CGI) scale.
**CHROMIUM AND PMDD**

- **Results:** Overall, chromium treatment was associated with reduced mood symptoms and improved overall health satisfaction.
- Chromium alone was associated with marked clinical improvement.
- Chromium plus antidepressant resulted in greater improvement than either chromium alone or antidepressant alone.
- **Conclusion:** Preliminary observations suggest chromium may be a useful monotherapy or adjunctive therapy for women suffering significant menstrual cycle-related symptoms.
- Larger controlled studies are needed to evaluate the efficacy of chromium treatment.

*J Diet Suppl* 2013 Dec;10(4):345-56
Does Lavender (Lavandula angustifolia) aromatherapy alleviate premenstrual emotional symptoms?

○ Randomized crossover trial
○ Investigated soothing effects of aromatherapy on PMS symptoms using lavender from the perspective of autonomic nervous system function
○ 17 women with mild to moderate PMS symptoms were examined on 2 separate occasions (aroma and control trials) in the late-luteal phases.
○ Two kinds of aromatic stimulation used: lavender and water as control
○ Experiment measured heart rate variability (HRV) reflecting autonomic nerve activity and the Profile of Mood States (POMS) as a psychological index before and after aromatic stimulation

Matsumoto et al. BioPsycholSocial Medicine 2013, 7:12
Does Lavender (Lavandula angustifolia) aromatherapy alleviate premenstrual emotional symptoms?

- Results: 10 minute inhalation of lavender scent significantly increased the high frequency (HF) power reflecting parasympathetic nervous system activity compared to control group (water).
- In addition POM tests revealed that inhalation of aromatic lavender oil significantly decreased two POMS subscales, depression and confusion.
- Conclusions: Lavender aromatherapy as a potential therapeutic modality for alleviating premenstrual emotional symptoms, which may be partially attributable to improvement of parasympathetic nervous system activity.

Matsumoto et al. BioPsychoSocial Medicine 2013,7:12
A systematic review looking at 8 studies with 9 different interventions identified

Acupuncture treatment sessions ranged from 2 to 13 sessions and treatment periods varied from both luteal and follicular phases to only luteal phase

Studies comprised of Korean acupuncture technique, TCM method with auricular point Shenmen added, Korean hand acupuncture and moxibustion technique

On a study done in Korean acupuncture technique, SP6 and CV 6 were mainly used

Physical symptoms such as headache, cramps, backache, cold sweats, hot flashes, breast pain, swelling of hands and feet, and abdominal pain and bulging improved as much as 50.5%

No adverse events reported

Jang et al. BMC Complementary and Alternative Medicine 2014, 14:11
ACUPUNCTURE
THAT’S ODD... MY NECK SUDDENLY FEELS BETTER...

EARLY ACUPUNCTURE
**POWER OF EXERCISE**

- RCT assessing effect of aerobic exercise on premenstrual symptoms in young women
- 30 participants aged 16-20 with PMS randomly assigned into two groups
- Control group received B6 and Calcium supplementation once daily
- Study group received the same medical treatment and participated in treadmill training 3/week x 3 months
- Premenstrual syndrome questionnaire (MSQ), complete blood work, and hormone assays performed at the start and after the treatment course

POWER OF EXERCISE

- Results: The study group showed a significant decrease in all post-treatment subscale symptoms.
- Hemoglobin, hematocrit, red cell count, and platelet count were significantly increased.
- Also a significant decrease in prolactin, estradiol and progesterone levels was discovered.
- Conclusion: Aerobic exercise via means of hemodynamic and hormonal changes results in the improvement of fatigue, impaired concentration, confusion, and most premenstrual symptoms.

“Why it can take over 100 million sperm to fertilize one egg”
**Female Infertility**

- The World Health Organization defines infertility as “a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.”
- NICE guidelines state that "A woman of reproductive age who has not conceived after 1 year of unprotected vaginal sexual intercourse, in the absence of any known cause of infertility, should be offered further clinical assessment and investigation along with her partner."

http://www.who.int/topics/infertility/en/
Causes of female infertility

- Ovulatory disorders: 25%
- Endometriosis: 15%
- Pelvic adhesions: 12%
- Tubal blockage: 11%
- Other tubal abnormalities: 11%
- Hyperprolactinemia: 7%
- Other causes: 9%
- Unexplained: 10%
ACQUIRED FACTORS

According to the American Society for Reproductive Medicine (ASRM) it is important to access acquired factors including:

- Age
- Smoking
- Sexually Transmitted Infections
- Weight

Seifer DB et al., Age-specific serum anti-Mullerian hormone values for 17,120 women presenting to fertility centers within the United States. Source: *Fertility and Sterility* (DOI: 10.1016/j.fertnstert.2010.10.011); Copyright © American Society for Reproductive Medicine *Terms and Conditions*
VITAMIN D

- Vitamin D is a steroid hormone
- Approximately 80-90% of vitamin D is produced in the skin after sunlight exposure
- A small amount of the body’s total vitamin D is also derived from diet
- Vitamin D deficiency is highly prevalent among women of reproductive age
- Increasing prevalence caused by obesity, changes in lifestyle, and reduced sun exposure
- There is evidence to support that Vitamin D modulates sex steroid hormones as well as reproductive processes in women and men
- Vitamin D receptor (VDR) and vitamin D metabolizing enzymes are found in human reproductive tissues

VITAMIN D

- Vitamin D has been associated with better in-vitro fertilization outcome, PCOS, endometriosis, primary dysmenorrhea, uterine leiomyoma, and ovarian reserve in late reproductive aged women.
- In the past year, several observational studies reported better in-vitro fertilization outcomes in women with sufficient vitamin D levels (>30ng/ml), mainly attributed to vitamin D effects on the endometrium.
- One RCT found an increased endometrial thickness in women with PCOS receiving vitamin D during intrauterine insemination cycles.
- Vitamin D supplementation had a beneficial effect on serum lipids in PCOS women.

VITAMIN D

- Vitamin D treatment improved endometriosis in a rat model and increased vitamin D intake was related to a decreased risk of incident endometriosis.
- Merhi et al. investigated the association between circulating 25(OH)D and anti-mullerian hormone (AMH) levels in a cross-sectional study including 388 premenopausal women with regular menstrual cycles.
- Authors observed a positive independent association of 25(OH)D levels with AMH in women aged at least 40 years (n=141).
- Vitamin D deficiency might be associated with lower ovarian reserve in late reproductive aged women.

LEPIDIUM MEYENII
(MACA)

- Cruciferous plant cultivated exclusively at an altitude of 4,000-4,500 m in the Peruvian Central Andes
- Different types of maca have different biological properties
- Experimental studies indicate effects of maca on nutrition, fertility, memory, energy, and mood
- Exact mechanisms of action are still unclear
- Has been used for centuries in the Central Andes of Peru and no toxic effects have been reported if it was consumed after boiling
- Recommended dose: 1,500 to 2,000 mg maca extract

Gonzalez, Gustavo Evidence-Based Complementary and Alternative Medicine Volume 2012, Article ID 193496
FEMALE REPRODUCTIVE LIFESPAN

- Fertility in women is known to precipitously decline after the age of 35.
- With advancements in medical care, a woman’s life expectancy has been prolonged by as much as 30 years over the past century.
- The age of menopause has changed by a meager 3-4 years during this same time period.
- This has created an anomaly in which the reproductive lifespan of women has become strikingly short in context of overall lifespan.
- Furthermore, we are seeing a growing trend of postponing childbearing, bringing the age-related decline in fertility to the forefront of reproductive medicine.

FEMALE REPRODUCTIVE LIFESPAN

- Biologically, the age at which menopause occurs is determined by the progressive decline and ultimate depletion of the ovarian oocyte-containing follicle reserve.
- Concomitantly is the diminishing quality of oocytes evidenced by an increase in chromosomal and spindle abnormalities and mitochondrial dysfunction.
- These changes significantly contribute to the extremely poor success of natural and assisted fertility attempts for women of advanced reproductive age and to the increased incidence of chromosomal anomalies when conception is successful.

FEMALE REPRODUCTIVE LIFESPAN

- An effective and realistic strategy for significantly delaying ovarian aging or improving oocyte quality has yet to be developed
- Changes in dietary patterns of humans over time may provide insight into novel avenues for delaying ovarian aging
- Anthropological studies have shown a remarkable change in the human diet over the past 100 years
- Most notably with regard to the type and amount of fat consumed
- Both an absolute and relative change in the omega-6 and omega-3 fatty acid consumption

FEMALE REPRODUCTIVE LIFESPAN AND OMEGA-3

- Historically our ancestors consumed a diet of omega-6 to omega-3 fatty acid ratio of 1:1
- Today the Western diet provides a ratio as high as 25:1
- This change is relevant given that the shift in dietary habits over the last 100 years is accompanied by a concurrent downward trend in fertility rates for women over the age of 35

PROLONGING THE FEMALE REPRODUCTIVE LIFESPAN AND IMPROVING EGG QUALITY WITH DIETARY OMEGA-3 FATTY ACIDS

Purpose:
➢ Evaluate the effect of omega-3 rich diet on murine reproductive function and egg quality
➢ Determine whether a diet rich in omega-3 fatty acids is safe for long-term consumption

Design:
➢ Omega-3 fatty acid-rich diet to mimic the fatty acid composition of cold water fish with omega-3 to omega-6 ratio of 20:1 provided as DHA and AA
➢ Omega-6 fatty acid-rich diet to mimic the standard Western diet with fat provided as soybean oil with omega-6 to omega-3 ratio of 8:1 provided as linoleic acid and alpha-linoleic acid
➢ Control for essential fatty acid deficiency in which all fat was provided as hydrogenated coconut oil

Prolonging the female reproductive lifespan and improving egg quality with dietary omega-3 fatty acids

Design:

➢ Breeding trials were performed to characterize reproductive potential of animals on these diets during normal murine female reproductive span
➢ Adult females were randomized to one of the three different diets (HCO, SOY, DHA)
➢ Following 4 weeks of treatment, breeding trials were initiated on the FO generation

Results:

➢ Animals on the SOY diet were bred to the F3 generation
➢ Animals on the DHA to the F6 generation
➢ Animals on HCO diet were not able to successfully reproduce beyond the F1 generation likely secondary to severe essential fatty acid deficiency
➢ DHA diet had improvement in offspring survival in later generations (75% F1, 95% F5, and 100% F6)

Prolonging the Female Reproductive Lifespan and Improving Egg Quality with Dietary Omega-3 Fatty Acids

- Animals on their specific diets then tested for ability to reproduce at advanced maternal age (>10 months)
- All animals on omega-3 rich diet (7) were able to successfully reproduce with an average of 3.3 liters b/t 10 and 15 months of age
- Although liter was smaller (4.4) compared to younger cohorts of animals (6.0) on the same diet (P=0.10), the overall survival of offspring was 89%
- None of the 10 aged animals on omega-6-rich diet had any viable litters
- For comparison, breeding trials on 10 months of age were initiated for animals on standard laboratory rodent chow, and there were only two animals that had one viable liter each

PROLONGING THE FEMALE REPRODUCTIVE LIFESPAN AND IMPROVING EGG QUALITY WITH DIETARY OMEGA-3 FATTY ACIDS

Conclusions:

➢ Lifelong consumption of a diet rich in omega-3 fatty acids prolongs murine reproductive function into AMA
➢ A diet rich in omega-6 fatty acids is associated with very poor reproductive success at AMA.
➢ Short-term dietary treatment with a diet rich in omega-3 fatty acids initiated at the time normal age-related rapid decline in murine reproductive function is associated with improved oocyte quality
➢ Short-term dietary treatment with omega-6 fatty acids results in very poor oocyte quality
➢ Thus, omega-3 fatty acids may provide an effective and practical avenue for delaying ovarian aging and improving oocyte quality at AMA

MTHFR Polymorphisms

- Folate has a crucial role in human reproduction
- Folate deficiency can compromise the function of the metabolic pathways it is involved in, leading to accumulation of homocysteine
- The gene MTHFR encodes the 5-MTHFR enzyme involved in folate metabolism
- Polymorphisms of this gene (C677T and A1298C) are related to decreased enzyme activity and consequent changes in homocysteine concentration
- Folate deficiency and hyperhomocysteinaemia can also compromise fertility and lead to pregnancy complications by affecting development of oocytes, preparation of endometrial receptivity, implantation of embryo, and pregnancy
- In folliculogenesis, hyperhomocysteinaemia can activate apoptosis, leading to follicular atresia and affecting the maturity of oocytes and quality of embryos cultured in vivo

Reproductive Biomed Online, 2014 Jun;28(6):733-8
MTHFR Polymorphisms

- MTHFR testing available both serum and saliva

- Encourage appropriate folate supplementation (methylfolate) in all women of child-bearing age

- Consider increasing recommended dose based on MTHFR status (400mcg vs 800mcg vs other) and risk factors