

Herbal Management of Complex Reproductive Challenges in the Premenopausal Woman

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The Delicate Balance

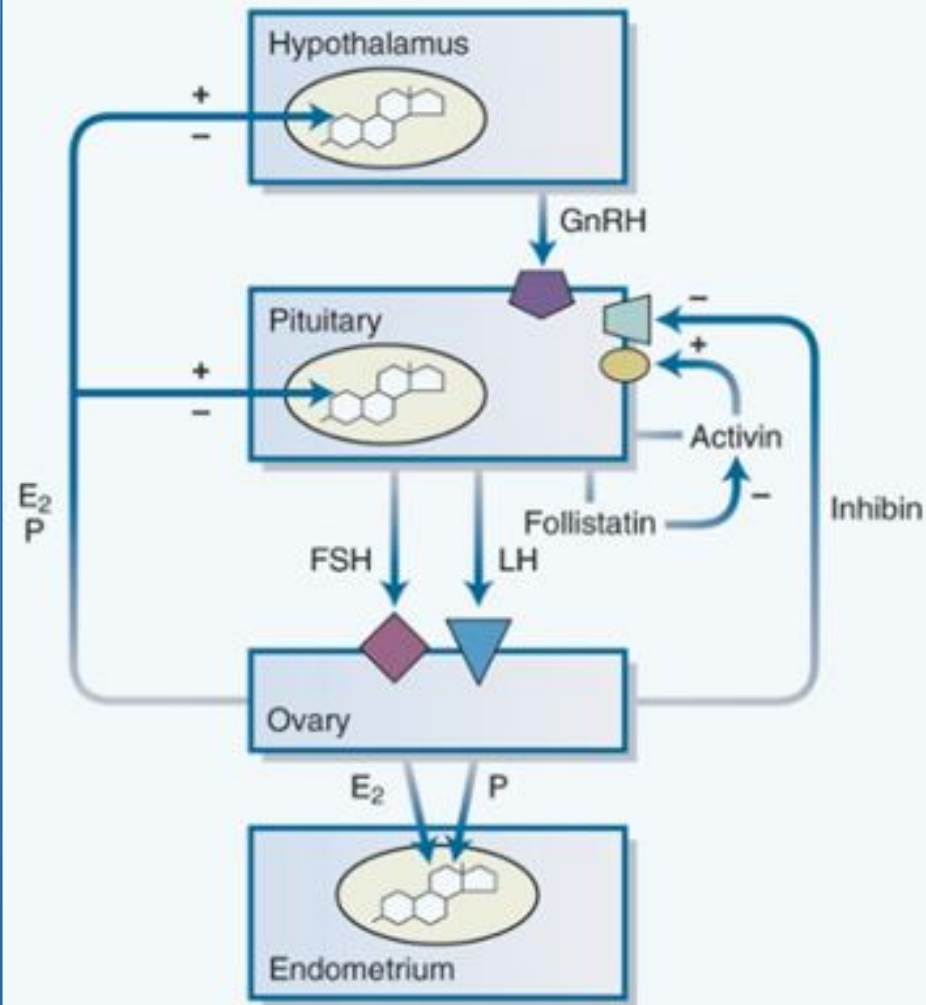
The female reproductive function from puberty to menopause can be viewed as an extremely delicate ticking clock

- Depends on tightly coordinated functions of the hypothalamus, pituitary, ovaries, and endometrium



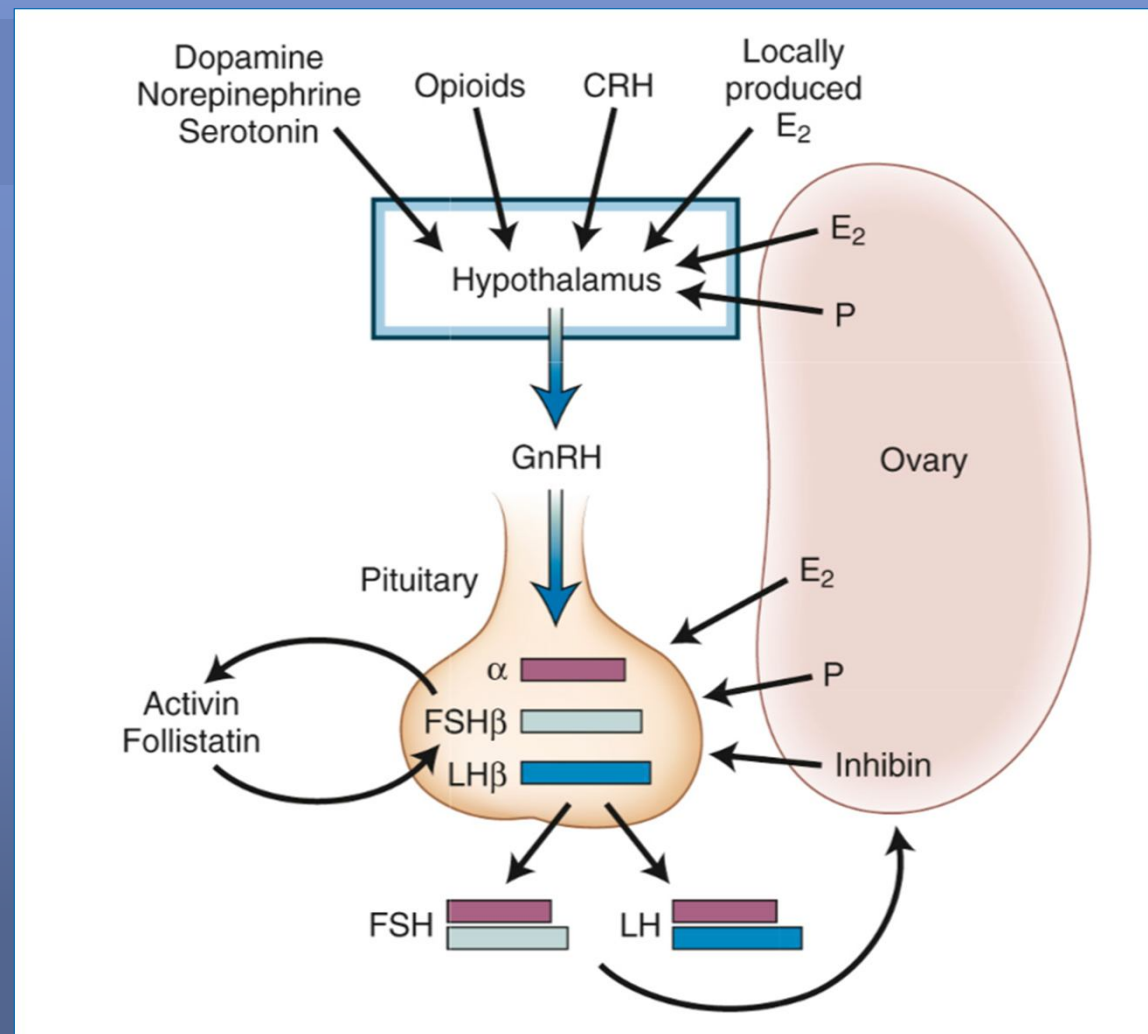
- Cyclic, predictable menses and regular ovulation

Melmed S, Polonsky KS et al. *Williams Textbook of Endocrinology* 13th edition, 2016 Elsevier, Philadelphia. ISBN-13: 9780323297387. pp590-663



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Hormone Regulation



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Phytotherapy for a Healthy Female Reproductive System

Key herbs:

- Shatavari
- White Peony
- Schisandra
- Chaste Tree
- Tribulus



Shatavari



"She who possesses a hundred husbands"

- Traditionally Shatavari is regarded as a female reproductive tonic with **rejuvenative** action and as a tonic for general health and fatigue
- It has been used to support conception and to alleviate menopausal discomfort¹
- Contains steroidal saponins,² which support a subtle estrogen modulating activity

1. Frawley D. Lad V. *The Yoga of Herbs: An Ayurvedic Guide to Herbal Medicine*, 2nd Edn. Lotus Press, Santa Fe, 1988

2. Hayes PY et al. Steroidal saponins from the roots of *Asparagus racemosus*. *Phytochemistry* 2008; **69**: 796

Shatavari

- Promotes general well-being and resistance to occasional stress
- Promotes estrogen balance
- Relieves menopausal symptoms and discomfort
- Improves vitality
- Relieves dryness of tissue including the reproductive system

White Peony

- Licorice and White Peony are used in traditional Chinese and Japanese medicine to support normal female:
 - Testosterone levels^{1,2,3,4}
 - Prolactin levels^{1,3}
 - Estrogen levels¹
 - Conception⁴



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1. Takahashi K et al. Effect of TJ-68 on polycystic ovarian disease. *Int J Fertility and Menopausal Stud* 1994; **39**: 69
2. Yaginuma T et al. Effects of traditional herbal medicines on serum testosterone levels and induction of regular ovulation in hyperandrogenic and oligomenorrheic women. *Nippon Sanka Fujinka Gakkai Zasshi*; **34**(7): 939-944
3. Yan HN et al. *J Clin Psycholarmacol* 2008; **28**(3): 264-270
4. Takahashi K et al. Effects of traditional medicine on testosterone secretion in patients with polycystic ovarian syndrome detected by ultrasound. *Nippon Sanka Fujinka Gakkai Zasshi* 1988; **40**(6): 789-796

Schisandra

- Schisandra lignans enhanced phase I/II hepatic metabolism when administered orally (*in vivo*)¹⁻³
 - Supported the metabolism of estradiol²
 - Supported metabolism of alcohol⁴
 - Supported ethanol-induced oxidative stress^{5,6}
- Schisandra lignans support normal hepatocellular defenses³



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2. Lu H, Liu GT. *Chung Kuo Yao Li Hsueh Pao* 1990; **11**: 331
3. Ip SP et al. Effect of schisandrin B on hepatic glutathione antioxidant system in mice: protection against carbon tetrachloride toxicity. *Planta Med* 1995; **61**: 398
4. Lee JS, Lee SW. *Korean J Dietary Culture* 1990; **5**: 259
5. Lu H Liu GT. *Chem Biol Interact* 1991; **78**: 77
6. Lam PY et al. Schisandrin B co-treatment ameliorates the impairment on mitochondrial antioxidant status in various tissues of long-term ethanol treated rats. *Fitoterapia* 2010; **81**: 1239

Chaste Tree



Clinical support for dopaminergic activity:¹

- Supported healthy prolactin levels
- Balanced menstrual cycle
- Eased the discomfort associated with PMS

Clinical support for melatonin activity:²

- Chaste Tree supported melatonin by approximately 60% and improved sleep quality in 20 healthy males aged 20 to 32 years

1. Milewicz A, Gejdel E, Sworen H et al. *Arzneim-Forsch* 1993; **43**(7): 752-756

2. Dericks-Tan JS et al. *Experimental and Clinical Endocrinology & Diabetes* 2003; **111**: 44-46

Tribulus

- *Tribulus terrestris* extract taken on days 5-14 of the menstrual cycle for 2-3 months supported ovulation (67%)¹
- Clinical study evaluated the effects of epimestrol, Tribulus and cyclofenil on ovulation induction in women with oligo/anovulation¹
 - During the 3 month follow-up ovulation rates were 74%, 60% and 24% respectively ²



1. Dericks-Tan JS et al. *Experimental and Clinical Endocrinology & Diabetes* 2003; **111**: 44-46
2. Arentz S, Abbott JA, Smith CA et al. *BMC Complement Altern Med* 2014; **14**: 511. PMID: 25524718

Phytotherapy for a Healthy Female Reproductive System

Additional support – adrenals:

- Licorice
- Rehmannia

• Additional support – nervous system, adaptogens:

- St John's Wort
- Saffron
- Skullcap
- Schisandra
- Withania
- Korean Ginseng



Complex Reproductive Conditions

- Functional hypothalamic amenorrhea
- Uterine fibroids
- Polycystic ovary syndrome

Functional Hypothalamic Amenorrhea

- Usually have a history of regular menses for some period after menarche
- Amenorrhea of 6 months duration
- Usually normal body weight or thin
- Involves aberrant but reversible regulation of neuroendocrine pathways

Functional Hypothalamic Amenorrhea

Three major types:

- Stress induced
- Exercise induced
- Weight loss related
eg dieting, eating disorders

Also:

- Chronic illness
- Medication that alters neurotransmitters



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Stress and FHA

HPA axis dysfunction:

- Common in many women with functional hypothalamic amenorrhea (FHA)
- Increased CRH, ACTH, cortisol
- Daytime cortisol levels may be elevated
- Pituitary response to CRH blunted



Exercise Induced FHA

- Regular vigorous exercise can lead to menstrual disturbances, a delay in menarche, luteal phase dysfunction, and secondary amenorrhea
- Competitive athletes show endocrine abnormalities in the central nervous system
- Abnormalities include elevations of central CRH and β -endorphin levels
- The intensity, length, and type of the sport determine severity
- Middle-distance, long-distance running, competitive swimming, gymnastics and ballet dancing

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Eating Disorders and FHA

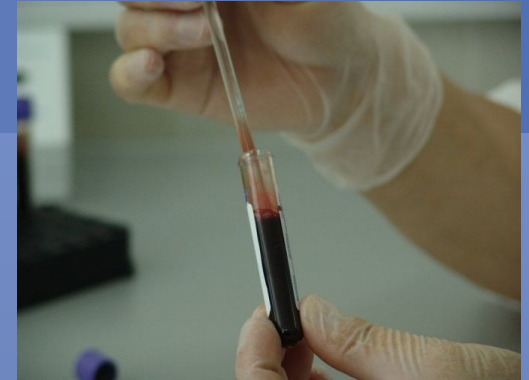
- Patients with anorexia nervosa and bulimia exhibit hyperactivation of the HPA axis
- Persistent hypersecretion of cortisol occurs throughout the day, although the diurnal variation is maintained
- Levels of CRH and β -endorphin are increased in the central nervous system
- Anovulation can persist in up to 50% of anorexic patients, even after normal weight is achieved

Eating Disorders and FHA

- In anorexia nervosa, basal metabolism is decreased
 - Peripheral conversion of T_4 to T_3 is decreased
 - Instead, T_4 is converted to reverse T_3

Tests

- hCG - to check for pregnancy
- FSH, LH, estrogen, testosterone, progesterone
- Prolactin
- Cortisol
- Thyroid – TSH, fT3, fT4
- Insulin - if there is central body fat



Management of Patients with FHA

- Deal with primary cause:
 - Support HPA axis, stress response
 - Adaptogens – Ashwagandha, Rhodiola, Schisandra
 - Adrenal tonics – Licorice, Rehmannia
 - Nervous system tonics – St John's Wort, Saffron, Skullcap
 - Support healthy hormone balance
 - Shatavari, White Peony, Tribulus
- Reduction of exercise if applicable
- Correction of weight loss where necessary



Uterine Fibroids

- Benign tumors also known as uterine leiomyomas or myomas
- Occur in approximately 80% of women¹
- Many women will be asymptomatic
- Severe symptoms develop in 15 to 30% of cases²
- Majority diagnosed in women between the ages of 28 and 52 years³

1. Manta L, Suciu N, Toader O et al. *J Med Life* 2016; **9**(1): 39-45. PMID: 27974911

2. Melmed S, Polonsky KS et al. *Williams Textbook of Endocrinology* 13th edition, 2016 Elsevier, Philadelphia. ISBN-13: 9780323297387. pp590-663

3. Aleksandrovych V, Bereza T, Sajewicz M et al. *Folia Med Cracov* 2015; **55**(1): 61-75. PMID: 26774633

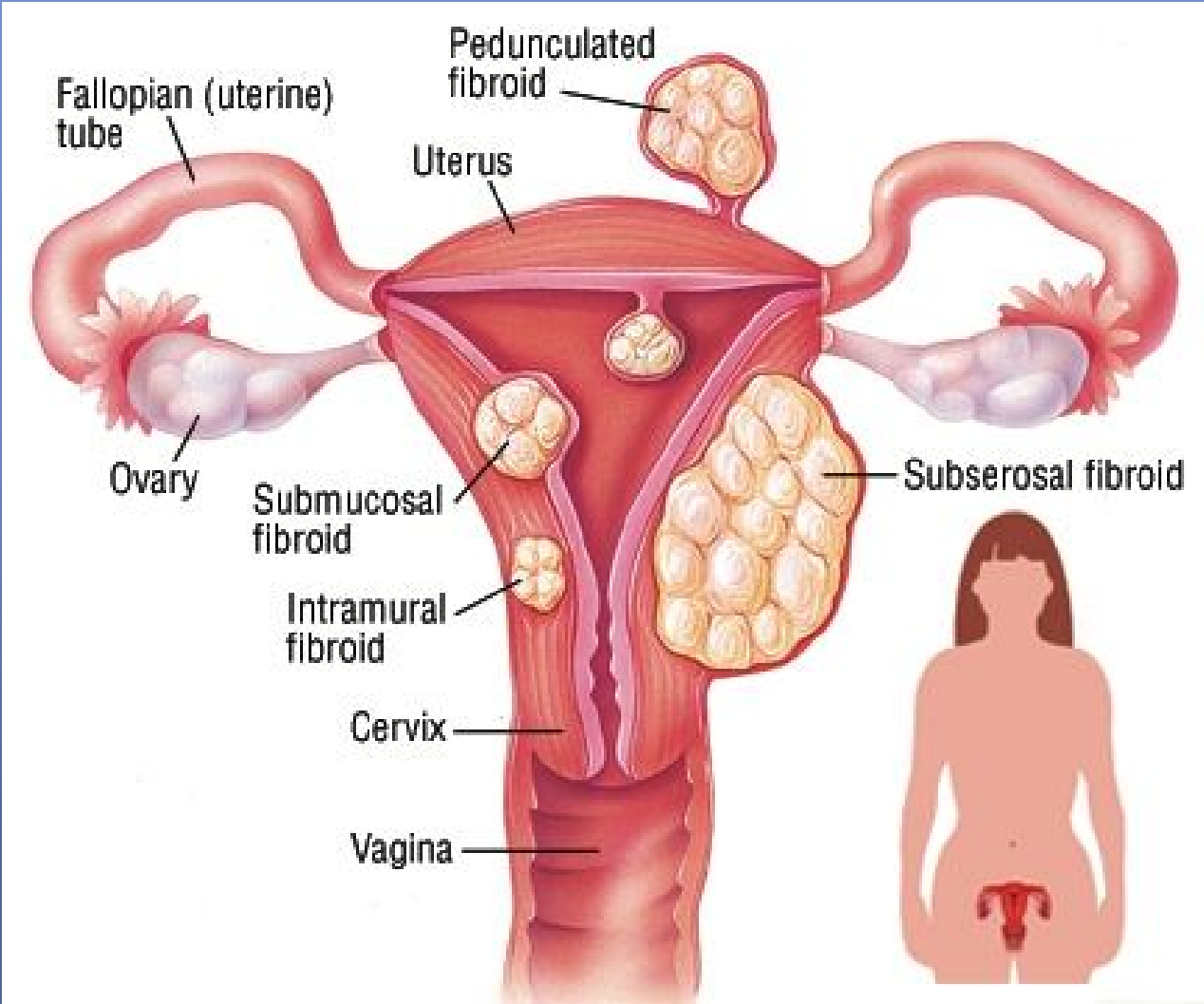
Uterine Fibroids

- Appears to be increased growth of fibroids during perimenopause
- Possibly due to changes in estrogen/progesterone balance, increasing LH and hormonal fluctuations



Classification

- Four main classifications based on location in the uterus
 - Subserous (located just beneath the serosal surface)
 - Intramural (found primarily within the myometrium)
 - Submucous (located beneath the endometrium)
 - Pedunculated (grow on a small stalk that connects them to the inner or outer wall of the uterus)
- Intramural are the most common type of fibroid



Risk Factors

- Ethnicity - black skinned races have higher risk
- Early menarche
- Nulliparous women
- Obesity, insulin resistance¹
 - Can lead to increased estrogens and decreased SHBG²
- Caffeine and alcohol consumption
- Chronic inflammation³
- Exposure to endocrine-disrupting chemicals (EDCs)³



1. Manta L, Suci N, Toader O et al. *J Med Life* 2016; **9**(1): 39-45. PMID: 27974911

2. Aleksandrovych V, Bereza T, Sajewicz M et al. *Folia Med Cracov* 2015; **55**(1): 61-75. PMID: 26774633

3. Katz TA, Yang Q, Treviño LS et al. *Fertil Steril* 2016; **106**(4): 967-77. PMID: 27553264

Etiology

- Not completely understood¹
- Under the influence of ovarian hormones
- Estrogen and its ER α stimulates the growth of fibroids²

1. Manta L, Suciu N, Toader O et al. *J Med Life* 2016; **9**(1): 39-45. PMID: 27974911

2. Melmed S, Polonsky KS et al. *Williams Textbook of Endocrinology* 13th edition, 2016 Elsevier, Philadelphia. ISBN-13: 9780323297387. pp590-663

Symptoms

- Symptoms depend on size, location and number of fibroids
- The majority of women are asymptomatic, up to 60% depending on ethnicity
- Menorrhagia, prolonged uterine bleeding
- Pressure, urinary incontinence, constipation¹
- Pelvic pain, dysmenorrhea
- Anemia²
- Clotting during menstrual bleed, spontaneous heavy bleeds

1. Aleksandrovych V, Bereza T, Sajewicz M et al. *Folia Med Cracov* 2015; **55**(1): 61-75. PMID: 26774633

2. Sato S, Maekawa R, Yamagata Y et al. *Sci Rep* 2016; **6**: 30652. PMID: 27498619

Fertility/Pregnancy Outcomes

- Infertility, miscarriage
- Infertility is most likely to occur with submucosal fibroids and can be due to:
 - Distortion of the endometrial cavity
 - Obstruction of fallopian tubes or cervix
 - Alteration of the endometrium
 - Vascular changes that reduce implantation
- Pre-term birth may be associated with subserous and submucosal fibroids
- **However most women will have normal pregnancy outcomes**



Aleksandrovych V, Bereza T, Sajewicz M et al. *Folia Med Cracov* 2015; **55**(1): 61-75. PMID: 26774633

<https://pixabay.com/en/newborn-kid-newburn-dream-sleepy-1328454/>

Diagnosis

- Abdominal or transvaginal ultrasonography
- Transvaginal ultrasonography is a sensitive method for determining the size, number and location of fibroids

Medical Treatment

- Hysterectomy is most often used for definitive treatment
- Myomectomy is used when preservation of childbearing capability is desired
- Intracavitary and submucosal fibroids can be removed by hysteroscopic resection
- Uterine artery embolization
- Endometrial ablation

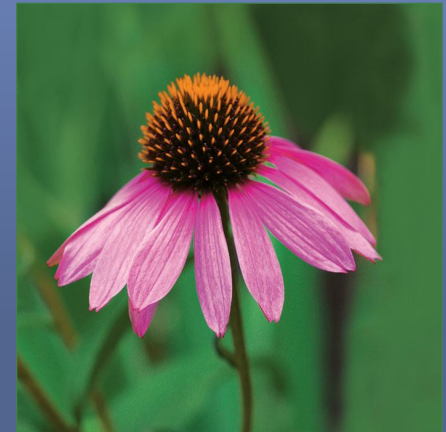


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<https://pixabay.com/en/surgery-action-hospital-doctor-1822458/>

Key Support for Women With Fibroids

- Shepherd's Purse
- White Peony
- False Unicorn
- Dong Quai
- *Echinacea angustifolia*, *E. purpurea* root



Support for Healthy Hormonal Balance

- Shatavari
- White Peony
- Schisandra
- Rosemary
- Milk Thistle



Support for Iron Deficiency

- Iron amino acid chelate
- Codonopsis
- Nettle leaf
- Licorice
- Ashwagandha
- Ginger
- Vitamins
 - C, B3, B6, B12



Support for Pain Relief

- Corydalis
- Raspberry leaf
- Wild Yam
- Cramp Bark
- Ginger
- California Poppy
- Jamaican Dogwood



Polycystic Ovarian Syndrome

- One of the most common endocrine dysfunctions in women
- A combination of reproductive and metabolic abnormalities (eg insulin resistance)
- Leading to hyperandrogenism and increased estrogen concentration¹
- Affects 2-18% of reproductive-aged females

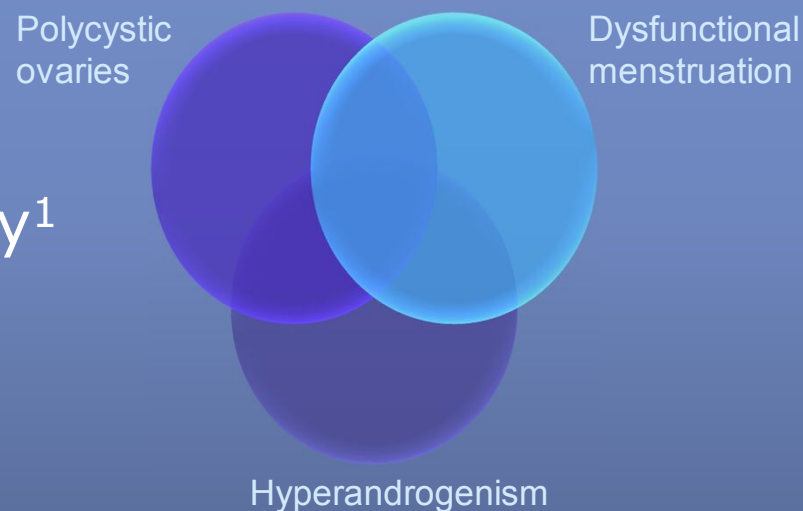
1. Thornton EC, Von Wald T, Hansen K. *S D Med* 2015; 68(6): 257-261. PMID: 26137726

Comparison of Diagnostic Guidelines

	Hyperandrogenism	Oligo- or Anovulation	Polycystic Ovaries
NIH Statement (1990)	✓	✓	
Rotterdam Criteria (2003) (2 out of 3)	✓	✓	✓
Androgen Excess Society (2006) (2 out of 3 - must include hyperandrogenism)	✓	✓	✓

Rotterdam Criteria

- Endorsed
 - In 2012 by an NIH workshop
 - In 2013 by the Endocrine Society¹
 - Used in most PCOS studies



1. Carmina e. Campagna AM, Fruzzetti F et al. *Endocr Pract* 2016; **22**(3): 287-293. PMID: 26523627

Diagnosis

- Diagnosis is made using criteria and by excluding other disorders in women with chronic anovulation and androgen excess
- Biochemical evidence of insulin resistance or glucose intolerance is not necessary for the diagnosis of PCOS
- However glucose intolerance should be investigated

PCOS Phenotypes

- Four different PCOS phenotypes (based on the Rotterdam definition) have been proposed:¹
 - a. Hyperandrogenism + oligomenorrhea + polycystic ovaries (H + O + P)
 - b. Oligomenorrhea + hyperandrogenism (O + H)
 - c. Hyperandrogenism + polycystic ovaries (H + P)
 - d. Oligomenorrhea + polycystic ovaries (O + P)
- Prevalence of each phenotype²
 - a. 52.8%, d. 29.7%, c. 13.7%, b. 3.8%

1. Shroff R, Syrop C et al. *Fertil Steril* 2007; **88**(5); 1389-1395. PMID 17462641

2. Jamil AS, Alalaf SK, Al-Tawil NG et al. *Arch Gynecol Obstet* 2016; **293**(2): 447-56. PMID: 26408006

Androgenic Phenotypes

- Compared to others, androgenic phenotypes have:
 - Higher levels of CRP
 - Higher fasting blood glucose, worse glucose tolerance test
 - Increased incidence of insulin resistance
 - Increased rate of dyslipidemia and metabolic syndrome¹
 - Increased incidence of non-alcoholic fatty liver disease, independent of obesity and insulin resistance²
 - Correlation between testosterone levels and dyspareunia, pelvic/bladder pain, urinary urgency and nocturia³



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- 1.Çelik E, Türkçüoğlu I, Ata B et al. *J Turk Ger Gynecol Assoc* 2016; **17**(4): 201-208. PMID: 27990089
- 2.Jones H, Sprung VS, Pugh CJ. *J Clin Endocrinol Metab* 2012; **97**(10): 3709-16. PMID: 22837189
- 3.Sahinkanat T, Ozturk E, Ozkan Y et al. *Arch Gynecol Obstet* 2011; **284**(4): 879-84. PMID: 21107589

Polycystic Ovarian Syndrome

- Women with PCOS have increased risk of developing:
 - Cardiovascular disease, including adolescents¹
 - Type 2 diabetes
 - Endometrial cancer²
 - Depression, anxiety³



1. Patel SS, Truong U, King M et al. *Vascular Medicine* 2017; **22**(2): 85-95. PMID 28095749
2. Melmed S, Polonsky KS et al. *Williams Textbook of Endocrinology* 13th edition, 2016 Elsevier, Philadelphia. ISBN-13: 9780323297387. pp590-663
3. Akdağ Cirik D, Dilbaz B, Aksakal S et al. *Turk J Med Sci* 2016; **46**(6): 1846-1853. PMID: 28081337

Signs and Symptoms

- Characterized by a wide range of symptoms, which can occur in different combinations and with different intensity¹
 - Ovarian dysfunction
 - Irregular menstruation, amenorrhea
 - Hirsutism, virilization, acne, weight gain
 - Polycystic ovaries¹
- Women with PCOS often experience reduced sexual desire, arousal and lubrication, and dyspareunia²

1. Kowalczyk k, Franik G, Kowalczyk D et al. *Eur Rev Med Pharmacol Sci* 2017; **21**(2): 346-360. PMID: 28165551

2. Eftekhari T, Sohrabvand F, Zabandan N et al. *Iran J Reprod Med* 2014; **12**(8): 539-46. PMID: 25408703

Signs and Symptoms

In many cases may also have:

- Hypertension
- Nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH)
- Fully developed metabolic syndrome

Signs and Symptoms

- Insulin resistance, hyperinsulinemia
 - Frequently observed in lean and obese women with PCOS
 - More severe degrees of insulin resistance or impaired glucose tolerance in obese women with PCOS
 - Glucose levels may be normal due to elevated circulating insulin
 - Insulin levels should be checked

Etiology

- Not well understood
- Multifactorial¹
- Strong trend to aggregate in families suggests an underlying genetic basis²
- Chronic inflammation, oxidative stress – cause or effect?
 - Elevated pro-inflammatory cytokines, CRP³



1. Bachelot A. *Ann Biol Clin* 2016; **74**(6): 661-667. PMID: 27848917
2. Melmed S, Polonsky KS et al. *Williams Textbook of Endocrinology* 13th edition, 2016 Elsevier, Philadelphia. ISBN-13: 9780323297387. pp590-663
3. Liu M, Gao J, Zhang Y et al. *Clin Endocrinol (Oxf)* 2015 D; **83**(6): 913-22

Common Features

- Elevated:

- Androstenedione, testosterone
- 17-hydroxyprogesterone
- Estrone, estradiol
- LH (may not be raised in obese women with PCOS)
- DHEA, DHEAS
- Insulin (increases testosterone, suppresses SHBG)
- Glucose
- AMH

- Reduced:

- SHBG (reduced by approx 50%)
 - Leads to increased free testosterone, estrogen
 - Inhibited by testosterone, insulin
- FSH

Laboratory Tests

- hCG - used to check for pregnancy, negative in PCOS
- TSH - to rule out hypothyroidism
- FSH - will be normal or low with PCOS, LH - will be elevated
- LH/FSH ratio - normally about 1:1 in premenopausal women, but a ratio of greater than 2:1 or 3:1 may suggest PCOS
- Estrogens - may be normal or elevated
- Testosterone - total and/or free, usually elevated
- Androstenedione - may be elevated, SHBG - may be reduced

Laboratory Tests

- AMH - currently under investigation to help diagnose PCOS
- DHEAS - frequently elevated with PCOS
- Prolactin - will be normal or mildly elevated (possibly due to chronic estrogen exposure)
- Lipid profile - low HDL, high LDL and total cholesterol, elevated triglycerides
- Glucose (fasting) and/or a glucose tolerance test
- Insulin
- HbA1c - to check for diabetes

Non-laboratory Tests

- Ultrasound - transvaginal and/or pelvic/abdominal are used to evaluate enlarged ovaries
 - May be 1.5 to 3 times larger than normal
 - Characteristically have more than 12 follicles per ovary, with each follicle less than 10 mm in diameter
 - Often cysts have the appearance of a "pearl necklace"
 - These ultrasound findings are not diagnostic
- Laparoscopy may be used to evaluate ovaries, evaluate the endometrial lining of the uterus, and sometimes used as part of surgical treatment

Medical Treatment

- Lifestyle intervention with the addition of oral contraceptives and /or metformin
- OCP increases the risk of hypertension and CVD in young women
- Metformin side effects include:
 - Abdominal pain in 59%, diarrhea in 65%, nausea in 62%, vomiting in 30%, headaches in 42% and mood swings in 17% of women

Where to Start With Treatment?

- A **multidisciplinary** approach is emphasized in the evidence-based guidelines for management of PCOS
- Lifestyle intervention should be first-line treatment



Arentz S, Smith CA, Abbott JA et al. *Phytother Res.* 2017 Sep;31(9):1330-1340. PMID: 28685911

<https://pixabay.com/en/people-woman-exercise-fitness-2592247/>

Major Treatment Aims

- When the patient is overweight or obese, particularly in cases of insulin resistance, the number one goal must be WEIGHT LOSS
- Treat metabolic disturbances eg dysglycemia, insulin resistance and dyslipidemia
- Support healthy hormonal profile
- Reduce chronic inflammation
- Correct nutritional deficiencies eg vitamin D, chromium, magnesium, B complex vitamins, omega-3
- Support the HPA axis



Weight Loss

- A relatively low reduction in weight (5%) can improve problems such as insulin resistance, elevated androgens, reproductive system dysfunction and fertility¹
- Weight loss in obese PCOS adolescents reduced:
 - Testosterone, androstenedione, DHEA-S, cortisol² and AMH³



1. Faghfoori Z, Fazelian S, Shadnoush M et al. *Diabetes Metab Syndr* 2017; **S1871-4021** (17): 30011-5. PMID: 28416368
2. Reinehr T, Kulle A, Rothermel J et al. *Endocr Connect* 2017; **6**(4): 213-224. PMID: 28373267
3. Reinehr T, Kulle A, Rothermel J et al. *Clin Endocrinol (Oxf)* 2017; **87**(2):185-193. PMID: 28432801

Weight Loss

- Moderate supervised aerobic training for 12 weeks improved reproductive outcomes via modulation of adiposity:
 - Improved adiponectin and AMH
 - In anovulatory women there was an improvement in ovulation rate of 43.3% and a restoration of menstrual cycle (56.7%)¹
- Outcomes may be improved with inclusion of behavioral and psychological strategies eg goal setting, self-monitoring, cognitive restructuring, relapse prevention²

1. Al-Eisa E, Gabr SA, Alghadir AH. *J Pak Med Assoc* 2017; **67**(4): 499-507. PMID: 28420905

2. Brennan L, Teede H, Skouteris H et al. *J Womens Health (Larchmt)* 2017 Jun 1. doi: 10.1089/jwh.2016.5792. [Epub ahead of print] . PMID: 28570835

Coleus - Weight Management

Two U.S. clinical trials:

- Coleus helps mitigate weight gain^{1,2}
- Coleus group reported less fatigue and hunger and increased fullness¹
- Coleus impacted on body fat percentage, fat mass and bone mass²
- Both trials were R, DB, PC for 12 weeks and used Coleus extracts which delivered 50 mg of forskolin per day^{1,2}



1. Henderson S et al. *J Int Soc Sports Nutr* 2005; **2**(2): 54-62. PMID: 18500958
2. Godard MP et al. *Obes Res* 2005; **13**(8): 1335-1343. PMID: 16129715

Coleus - Weight Management

- In conjunction with a low calorie diet, Coleus improved serum insulin, insulin resistance and increased HDL
- Limited effects on weight loss, however dietary information obtained through different methods was inconsistent
- R, DB, PC trial for 12 weeks with 30 participants
- Extract containing 25 mg forskolin twice daily 30 minutes before meals

Coleus

- Coleus may also improve thyroid hormone production and secretion
- Other major actions include:
 - Hypotensive
 - Antiplatelet
 - Cardiotonic
 - Upper digestive tract stimulant



Management of Blood Glucose and Lipids

- Gymnema
- Milk Thistle
- Turmeric
- Boswellia
- Resveratrol



- Nigella
- Cinnamon
- Specific nutrients including chromium, zinc, magnesium, selenium, manganese, vitamins B3, B6, B12



Manage Chronic Inflammation

- Turmeric
- Bioavailable curcumin
- Boswellia



Support for Healthy Hormone Balance

Combination of Peony and Licorice (equal quantities) lowered testosterone in women with:

- PCOS
 - 75 g/daily of herbal combination
 - Serum testosterone was significantly reduced at 4 weeks
- Hyperandrogenism
 - 5-10 g/daily of herbal combination
 - Reduction in serum testosterone was not significant (small sample size)
 - Positive outcomes in 7 out of 8 participants



Support for Healthy Hormone Balance

Uncontrolled study evaluated effects of Tribulus extract on female sexual function

- Significant improvements were seen in desire, arousal, orgasm and satisfaction
- Free testosterone levels decreased, DHEA increased
- Extract delivered approximately 300 mg/day of protodioscin



Conclusion

- Female reproductive issues are among the most common conditions seen by health care professionals
- They are also among the most complex
- An up-to-date understanding of the pathophysiology of these conditions combined with a sound knowledge in herbal medicine gives us very powerful clinical tools and enables us to achieve very good clinical outcomes in many of our female patients



Questions



Appendix

Gymnema

- Supported healthy fasting blood glucose, HbA1c, glycosylated plasma protein, serum lipids, cholesterol
- Doses ranged from 6 to 13 g dried herb daily
- Length of trials ranged from 1 to 30 months¹⁻⁴
- 4 week trial – 2 g Gymnema taken 30 mins before meals = impacts fasting and postprandial blood glucose levels⁵

1. Balasubramaniam KB et al. *J Natl Sci Counc Sri Lanka* 1992; **20**: 81
2. Shanmugasundaram ER et al. *J Ethnopharmacol* 1990; **30**: 281
3. Baskaran K et al. *J Ethnopharmacol* 1990; **30**: 295
4. Joffe DJ, Freed SH. *Diabetes in Control Newsletter*, Issue 76 (1): 30 Oct 2001
5. Paliwal R et al. *Ethno Med* 2009;**3**: 133

Gymnema

- Gymnema group:
 - Decrease in body weight, BMI and VLDL
 - Prevented decrease in insulin sensitivity and compensatory hyperinsulinemia
- Placebo group – significant increase in body weight, waist circumference, LDL, insulin, insulinogenic index and a decrease in Matsuda index (rate of disappearance of plasma glucose)

Gymnema

- Possible mechanisms of action include:¹
 - Regeneration of pancreatic islet cells
 - Improved insulin secretion from the pancreas
 - Delayed absorption of glucose
 - Modulation of incretin activity, incretin-mimetic activity
- Significantly suppressed increase in body weight, serum lipids, insulin and leptin, adipose tissue and liver inflammation associated with a high fat diet (animal study)²

1. Tiwari P, Mishra BN, Sangwan NS. *Biomed Res Int* 2014; **2014**: 830285. PMID: 24511547

2. Kim HJ, Kim S, Lee AY et al. *Am J Chin Med* 2017 May 18: 1-20. doi: 10.1142/S0192415X17500434. [Epub ahead of print]. PMID: 28514906

Milk Thistle

- Many clinical trials using silymarin
- Improvements in:
 - HbA1c
 - Fasting blood glucose
 - Blood insulin levels
 - Total cholesterol, LDL, HDL
 - CRP, high-sensitivity CRP

Turmeric

- T2DM patients – compared to controls 2 g encapsulated turmeric (46 mg curcumin) + metformin
 - Lowered LDL (by 9%)
 - Lowered LDL/HDL ratio (by 16.6%)
 - Significantly reduced serum high-sensitivity CRP
 - Reduced plasma malonaldehyde (MDA)
 - No significant changes in fasting plasma insulin, IR, glucose/insulin ratio or other lipids
- Control group – metformin

Boswellia

- Participants 30-48 years-of-age, T2DM of greater than 4 yrs duration, fasting blood glucose in range of 7.7-13.8 mmol/L
- Boswellia gum resin, 900 mg/day, for 6 weeks
- Maintained oral hypoglycemic drug regimen, diet and activity levels
- Boswellia group compared to placebo group:
 - Improvements in total cholesterol, HDL, LDL, liver enzymes (ALT, AST)

Boswellia

- Boswellia, 900 mg/day, for 6 weeks, T2DM
 - Decreased blood glucose, increased plasma insulin
 - Did not change insulin resistance which was increased in control group

Resveratrol

- T2DM, 250 mg/day resveratrol for 3 months, continued oral hypoglycemic drugs
 - Significant reductions in HbA1c, systolic BP, total cholesterol¹
- T2DM, 5 mg/day resveratrol twice daily for 4 weeks
 - Improvements in insulin resistance, blood glucose, and delayed appearance of glucose peaks after a test meal²

1. Bhatt JK, Thomas S, Nanjan MJ. *Nutr Res* 2012; 32(7): 537-541. PMID: 22901562

2. Brasnyó P, Molnár GA, Mohás M et al. *Br J Nutr* 2011; **106**(3): 383-389. PMID: 21385509

Nigella

- Menopausal women – signs of MetS, 1 g Nigella seeds/daily for 2 months
 - Dyslipidemia, slightly elevated BP and blood glucose, average BMI of 28
- Nigella group compared to placebo group:
 - Decreased total cholesterol, LDL, triglycerides, Increased HDL
 - Significant reduction in fasting blood glucose
- One month after cessation of treatment, Nigella group tended to change towards pretreatment levels

Nigella

- 20 sedentary, overweight females, 2 g Nigella seeds/day, 8 weeks
 - Compared to exercise alone, Nigella + exercise significantly lowered LDL and raised HDL¹
- T2DM - other various trials have shown reductions in total cholesterol, LDL, triglycerides, fasting blood glucose, HbA1c, IR²⁻⁴

1. Farzaneh E et al. *Int J Prev Med* 2014; **5**(2): 210-216. PMID: 24627749
2. Bilal A. PhD thesis, University of Arid Agriculture, Rawalpindi, 2008.
3. Bamasa AO et al *Indian J Physiol Pharmacol* 2010; 54(4): 344-354. PMID: 21675032
4. Salem EM et al. *Saudi J Gastroenterol* 2010; 16(3): 207-214. PMID: 20616418

Cinnamon

- Meta-analysis 8 studies - 4 in T2DM, 3 in prediabetes, 1 in healthy individuals
- Effective dose - 3 g/day dried herb equivalent
 - Significantly lowered fasting blood glucose
 - The % decline was similar to that achieved by metformin (around 6%)

Cinnamon

- A 2013 systemic review and meta-analysis¹
 - Decreased blood glucose, total cholesterol, LDL, triglycerides
 - Moderately increased HDL
- DB, PC pilot study, women with PCOS, 8 weeks²
 - Improvement in insulin sensitivity and insulin resistance in treatment group. No change in placebo group
 - No change in BMI, estrogen or testosterone in either group

1. Allen RW, Schwartzman E, Baker WL et al. *Ann Fam Med* 2013; **11**(5): 452-459. PMID: 24019277

2. Arentz S, Abbott JA, Smith CA et al. *BMC Complement Altern Med* 2014; **14**: 511. PMID: 25524718

Cinnamon

Other studies in patients with T2DM:

- 1.8 g/day, 90 days
 - Reduced HbA1c¹
- 2 g/day, 12 weeks
 - Reduced HbA1c, systolic and diastolic BP²
- 2.4 g/day, 3 months
 - Reduced fasting blood glucose, HbA1c, triglycerides³

1. Crawford P. *J Am Board Fam Med* 2009; **22**(5): 507-512. PMID: 19734396

2. Akilen R et al. *Diabet Med* 2010; **27**(10): 1159-1167. PMID: 20854384

3. Lu T et al. *Nutr Res* 2012; **32**(6): 408-412. PMID: 22749176