Secondary Amenorrhea

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2. Any information and statements regarding dietary or herbal supplements have not been evaluated by the Food and Drug Administration and are not intended to diagnose, treat, cure, or prevent any disease.

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Amenorrhea Overview

- Normal menarche= 9-18
- 1.8-3% prevalence
- 20% of women with infertility
- Amenorrhea

  -no menses by age 14 in absence of growth or development of secondary sexual characteristics

  -no menses by age 16 regardless of the presence of normal growth and development with the appearance of secondary sex characteristics

  -menses has occurred but now ceased for 3 mo if a history of regular cycles and 6 mo if irregular

Secondary Amenorrhea Causes
4 compartments

- **Compartment I**
  Disorders of outflow tract or uterine target organ
- **Compartment II**
  Disorders of ovary
- **Compartment III**
  Disorders of the anterior pituitary
- **Compartment IV**
  Disorders of CNS (hypothalamic) factors

Secondary Amenorrhea

Evaluation

- Menstrual history
- Family history
- Medication history
- Review of systems
- Other endocrine system problems
- Chronic illness
- Anorexia/bulemia
- Chaotic/disordered eating; radical diets
- Malnutrition
- Excessive exercise
- Stress

Secondary Amenorrhea

Evaluation

- Physical exam

  Secondary sex characteristics

  Sexual maturity

  Weight

  Signs of hirsutism

  Skin-acne

  Head- hair loss

Secondary Amenorrhea

Evaluation Overview

- Tests: TSH, prolactin, pregnancy
- Progesterone challenge; E/P challenge
- Later considerations

  Imaging,FSH, LH

Step 1

- Pregnancy test, TSH, prolactin
- If elevated TSH- then **hypothyroid** and treat
- If positive pregnancy test- **make decisions r.e. pregnancy**
- If elevated prolactin- **determine if tumor**: imaging (x-ray of sella turcica; MRI)
- If all are normal- **progestational challenge test**

Progestational Challenge

- Purpose: Asses the level of endogenous estrogen and outflow tract competence
- 3 Methods:
  1. MPA 10 mg/day for 5 days
  2. OMP 300-400 mg x 5-7 days
  3. parenteral progesterone in oil (200 mg)

Outcomes:

1. Progesterone withdrawal bleed- bleeds within 2-7 days of conclusion of progesterone challenge- then **anovulation**
2. No withdrawal bleed-need to clarify target outflow problem or lack of estrogen proliferation of endometrium

Step 2

- Estrogen/progestogen for 21 days

Methods:

1. CEE 1.25 or estradiol 2 mg daily for 21 days + MPA 10 mg for the last 5 days
2. OCPs (use 30 mcg pill)

Outcomes:

No withdrawal bleed- defect in compartment I (endometrium, outflow tract)

If bleeds-assume normal compartment I; if no infection or trauma- now determine if ovaries contain a normal follicular function and if sufficient pituitary gonadotropins

Step 3

Purpose: determine if ovaries contain a normal follicular function and if sufficient pituitary gonadotropins

Methods: serum FSH, LH

Step 3

- Outcomes

  Elevated FSH/LH = (FSH> 20 IU/L)

  postmenopause/POF (< age 40)

  RARE:

  1. FSH/LH elevated- lung cancer

  2a. High of one and low of other

  2b. FSH elevated, low LH

  a. rare-gonadotropin-secreting pituitary adenoma

Step 3

- Outcomes

3. Elevated FSH/normal LH

Perimenopause-

remaining follicles are the least sensitive;inadequate inhibin; could get pregnant

4. Elevated FSH/LH-Resistant or insensitive ovary-

elevated gonadotropins despite ovarian follicles- either receptors absence or post receptor defect.

5. POF due to autoimmune disease-

developing follicles contain lymphocytes and plasma cells. Check thyroid antibodies; polyglandular syndrome?

Other: MG, ITP, RA, vitiligo, AI hemolytic anemia

Step 3

- Outcomes

  6. High FSH/LH-

  normal ovarian follicles- galactosemia and 17 hydroxylase deficiency (affects both ovaries and adrenal glands)

  absent secondary sexual development; hypertensive

Step 3

- Outcomes

  Normal gonadotropins

  Most common: **Hypothalamic amenorrhea**

  Rare: abnormal gonadotropin molecules; inherited disorder of gonadotropin synthesis

Step 3: Low gonadotropins

- **Low FSH/LH (or normal)**

  distinguish between pituitary compartment III) or CNS-hypothalamic (compartment IV)

  Imaging: if normal + normal prolactin

Specific disorders by compartment

- **Compartment I**

  Asherman's Syndrome 7%

  Other: Mullerian Anomalies, Testicular Feminization, infection

- **Compartment II**

  Abnormal chromosomes .5%

  Normal chromosomes 10.0%

  ex/ Turner's syndrome (45, X), XH gonadal dysgenesis, gonadal agenesis, resistant ovary syndrome, POF, radiation/chemotherapy

- **Compartment III**

  Prolactin tumors 7.5%

  ex/pituitary prolactin secreting adenoma

- **Compartment IV**

  Anovulation 28 %

  Weight loss/anorexia 10 %

  Hypothalamic suppression 10%

  Hypothyroidism 1.0%

Natural Treatment Interventions Overview

- Make an accurate diagnosis

  methodical work-up
- Understand underlying cause

  methodical work-up: hx/px, our evaluation steps
- Management: underlying cause, complications, disease prevention, general body support-organ specific, constitutional, mind/body

Natural Treatment Interventions

- The Healing Power of Nature
- First Do No Harm
- Identify and Treat the Cause
- Treat the Whole Person
- Physician as Teacher
- Prevention is the Best Cure
- Resonance
- Choice

Special needs/Management of premature menopause

- Grief over loss of fertility
- Discuss child bearing options
- Managing cancer side effects
- Treatment options for menopausal symptom relief
  - Hormonal contraception
  - Menopausal HT
- Treatment options for disease prevention
- Both emotional and physical issues

Premature Ovarian Failure

- **Address cause- environmental? AI? Genetic?**
- **Complications:** Estrogen deficiency symptoms, premature aging= ex/ osteoporosis, arteries, brain

1) MHT

2) OCP

Options: Hormone therapy until 51

Ex/ td estradiol patch 0.1 mg+OMP 200 mg/day or MPA 10 mg/day for 12 days/month

Ex/ Femring q 3 months (0.1mg)+OMP 200 mg/day or MPA 10 mg/day for 12 days/month

Ex/ Oral Estradiol 2 mg/day + OMP 200 mg/day for 12 days/mo

Ex/ OCP (EE 20 or 30 mcg/progestin pill; cyclic or continuous ; better to have cyclic regimen-easier to recognized the 5-10% chance for spontaneous pregnancy

(recent evidence demonstrated that 0.1 mg patch plus cyclic MPA was superior to a 30 mcg OCP in improving BMD in women with POI)

Try for 3-6 months but not more

4) poly glandular support

5) General mind/body support

6) Traditional follicular stimulants, emmenagogues

7) Rhodiola

8) Maca root

Premature Ovarian Failure
Environmental Influences

- Evaluation for exposure-
  occupational, location-childhood and adult,
  dental, diet, meds, etc
- Consider testing for exposure to toxic synthetic chemicals, solvents, pesticides and heavy metals
- Treat for environmental exposures

Premature Ovarian Failure Management

- **Disease Prevention**

  -Osteoporosis

  surveillance- DEXA

  Calcium/Magnesium/D/K/trace minerals

  Exercise-weight bearing

  Nutrition

  OCPs vs HRT vs BHRT

  -CAD- lifestyle, nutraceuticals, OCP vs HRT

  - Alzheimer's HRT vs OCP

  -Progressive estrogen deficiency problems- vaginal atrophy, skin aging, gums aging, bone loss, atherosclerosis, dyslipidemia, insulin resistance, weight gain and more …

Premature Ovarian Failure Sample Tx Plan

- **3-6 months**

  - Endocrine detox, whole foods diet

  - Flax seeds 1-2 tbsp per day

  - Soy – 1-2 servings per day

  - Combination formula: 2 caps daily

  (licorice, chaste tree, rhodiola, false unicorn, vervain, sarsparilla, wild yam, black cohosh)

  -- Black cohosh S.E. 40 mg bid

  -- Maca root 2 gm per day

  -- Bone/heart/brain support-lifestyle, nutraceuticals

cons/ Chaste tree 2 oz./ Partridge berry 2 oz/ Rhodiola 2 oz/

Yarrow 2 oz 2 tsp per day

POI- Management

Hormone replacement for young women with POI should mimic normal ovarian function as much as possible; and adequate doses of estrogen with adequate endometrial protection.

Options:

Ex/ td estradiol patch 0.1 mg+OMP 200 mg/day or MPA 10 mg/day for 12 days/month

Ex/ Femring q 3 months (0.1mg)+OMP 200 mg/day or MPA 10 mg/day for 12 days/month

Ex/ Oral Estradiol 2 mg/day + OMP 200 mg/day for 12 days/mo

Ex/ OCP (EE 20 or 30 mcg/progestin pill; cyclic or continuous ; better to have cyclic regimen-easier to recognized the 5-10% chance for spontaneous pregnancy

(recent evidence demonstrated that 0.1 mg patch plus cyclic MPA was superior to a 30 mcg OCP in improving BMD in women with POI)

Premature Ovarian Failure Alternate Tx Plan

- Oral contraceptives
  ex/ Lo Estrin 1/30
- HRT Estradiol 1 mg/OMP 100 mg per day
- HRT Estradiol 2 mg/OMP 200 mg per day
- Whole foods diet, flax seeds, soy
- Bone/Heart/Brain support= lifestyle, nutraceuticals

Anovulatory Amenorrhea

- When not related to PCOS or hypothyroid or hyperprolactinemia

Progesterone Precursors

- Herbs that contain diosgenin or sarsasapogenin
  - bloodroot (Sanguinaria canadensis)
  - blue cohosh (Caulophyllum thalictroides)
  - fenugreek (Trigonella foenumgraecum)
  - sarsaparilla (Smilax officinalis)
  - wild yam (Dioscorea spp)
  - yucca (Yucca spp)

Traditional Botanicals

- **Uterine Tonics: Dong quai (*Angelica sinensis*), Blue cohosh (*Caulophyllum thalictroides*), Crampbark (*Vibernum opulus*), False unicorn or helonias (*Chamalerium luteum*) and Squaw vine (*Mitchella repens*).**
- **Dong quai - improves the metabolism within the uterus[i] ; regulating hormonal control and improving the timing of the menstrual cycle.[ii]**
- **Blue Cohosh – improves muscular tone of a hypotonic uterus**
- **Crampbark- a uterine sedative and a uterine tonic.**
- **False unicorn or helonias- improve uterine tone and decrease "pelvic congestion".**
- **Squaw vine- uterine tonic that increases the circulation to, and in, the uterus thereby reducing uterine congestion. It can both sedate a hypertonic uterus as well as tonify a hypotonic uterus.**
- **Ginseng species- ability to enhance overall health, vitality, stamina and endurance. Siberian ginseng may be able to promote regulation of reproductive hormones thereby regulating the timing of ovulation.[iii]**

[i] Zhu D. Dong Quai. Am J Chinese Med 1986;XV(3-4): 117-125.

- [ii] Zhiping H, et al. Treating amenorrhea in vital energy-deficient patients with Angelica sinensis. J Trad Chin Med 1986;6(3):187-190.
- [iii] Darymov, L.V. On the gonadotrophic effect of Eleutherococcus glycosides. Lek. Srd. Dalinego Vostioka 1972;11:939-944.

Anovulation: Black Cohosh

- Similar to chaste tree, black cohosh (*Cimicifuga racemosa*) has been shown to stimulate pituitary secretion of LH and therefore lead to ovulation and subsequent production of progesterone by the corpus luteum.
- Black cohosh may be especially valuable for women in their 40's whose FSH levels may be starting to increasing as the ovary ages.

Planta Med 1985;1:46-49.
Planta Medica 1985;1:46-49.

Anovulation: Tribulus

- A plant that many are not familiar with, Tribulus, has been studied as an ovarian stimulant. Women taking Tribulus every day has demonstrated the ability to normalize ovulation whereby some of the women also became pregnant.[i]
- When using Tribulus simultaneously with an ovulation-induction drug, the results with the combined use were better than the drug by itself. [ii]

- [i] Chemical Pharmaceutical Research Institute. Sofia, Bulgaria.
- [ii] CLINICAL STUDY OF TRIBESTAN IN FEMALES WITH ENDOCRINE STERILITY Non published data. Sopharma clinical study

Rhodiola Rosea

Anovulation: Rhodiola rosea

- Egg maturation enhanced in rats
- Increased number of growing follicles, oocyte volumes and preparation of uterine mucosa for fertilization in sexually mature female mice
- No change when given to sexually immature female mice

Rhodiola rosea

- 40 women with amenorrhea
- Treatment: 100 mg bid for 2 weeks

  or 1ml rhodosin IM for 10 days.

  (Treatment cycle treated 2-4 times in some subjects)
- Normal menses restored in 25 women
- 11 of whom became pregnant

Proc Scientific Conference on Endocrinology and Gyn 1970

Vitex

Chasteberry [Vitex]

Vitex and PCOS (Review)[1]

- Evidence for an equivalent effect of pharmaceutical agent bromocriptine and Vitex agnus-castus.

  - **Lowers prolactin due to dopaminergic effects** [38-41,63] – 40 mg daily for 3 months
  - **Increased serum progesterone** [49,62] - 20mg daily for 3 months
  - **Improved pregnancy rates** [61,62**] - 20mg daily for 3 months

*Methodological shortcomings included not reporting baseline characteristics for subgroups and small sample sizes.

**Combined product Mastodynon: Vitex + Homeopathics (Made in Germany).

1. Arentz, S., Abbott, J. A., Smith, C. A., & Bensoussan, A. (2014). Herbal medicine for the management of polycystic ovary syndrome (PCOS) and associated oligo/amenorrhoea and hyperandrogenism; a review of the laboratory evidence for effects with corroborative clinical findings. *BMC Complementary and Alternative Medicine*, *14*, 511. http://doi.org/10.1186/1472-6882-14-511

Anovulation: Chaste Tree

- Chaste tree berry (*Vitex agnus-castus*) stimulates the release of luteinizing hormone (LH) from the pituitary gland and mildly inhibits FSH. The result is an indirect ability on the part of Vitex to raise or modulate progesterone levels.[i] Vitex also modulates the secretion of prolactin from the pituitary gland and in one study prolactin was significantly reduced while shortened luteal phases and progesterone deficits were normalized.[ii]
-

[i] Ther Gegenew 1965;104(9): 1263-1265.

- [ii] Arzneim-Forsch Drug Res 1993;43:752-756.

Vitex and Secondary Amenorrhea- Vitex

- N=57 women with a variety of menstrual disorders
- 6 of the women had secondary amenorrhea developed one or more cyclic menstruations

Probst V Roth O. Dtsch Med Wschr 1954

Vitex and Secondary Amenorrhea

n=20 x 6mo. 40 drops extract daily

15/20 had onset of menstrual cycles

Losh, Kayser. Gynakol Praxis 1990

Nutrition Flax Seeds

- N=18 normally cycling women
- Low fiber diet x 3 months
- Low fiber diet plus flax seeds (10 grams) x 3 months

Results: 3 anovulatory cycles in control

no anovulatory cycles during flax

Chronic anovulation (does not meet PCOS criteria)

Sample Treatment Plan

- Ground flax seeds 1-2 tbsp/day
-OMP 200 mg 12 days per month
-Progest/Progonol 1/4 tsp bid 2 weeks/2 weeks off
-Rhodiola 200 mg/day
-Symplex F 2-3/day
-Vitex: n=20 x 6mo. 40 drops extract daily
15/20 had onset of menstrual cycles

Losh, Kayser. Gynakol Praxis 1990

PCOS: DEFINITION

2003 Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop

- At least 2 of the following 3 features:
  - Oligo- or anovulation
  - Clinical and/or biochemical signs of hyperandrogenism
  - Polycystic ovaries (≥ 12 follicles 2-9 mm or vol > 10 ml)
- Exclusion of other etiologies

Diagnosis

- **Rotterdam criteria endorsed by National Institutes of Health (NIH).**
  - **Includes 2 of the following:**
    - Clinical and/or biochemical hyperandrogenism
    - Oligo-ovulation or anovulation
    - Polycystic ovaries
- **Androgen Excess Society (AES)**
  - **Includes all of the following:**
    - Clinical and/or biochemical hyperandrogenism
    - Ovarian dysfunction and/or polycystic ovaries

Epidemiology - PCOS

- Most common endocrine disorder of reproductive-aged women worldwide.
- Society for Reproductive Endocrinology and Infertility (SREI) states – 5-10% of women worldwide
- High Risk Groups:
  - Oligoovulatory infertility
  - Obesity and/or insulin resistance
  - Diabetes Type 1, 2, gestational
  - Premature adrenarche
  - 1st degree relatives
  - Use of antiepileptic drugs

Pathogenesis - PCOS

- Genetics
- Gonadotropin secretion and action
- Insulin secretion and action
- Weight and energy regulation
- Androgen biosynthesis and action
- Environmental factors

PCOS: MANAGEMENT

Treatment Goals

- Menstrual regularity/endometrial protection
- Reduce androgens/treat symptoms of excess
- Restore fertility if desired
- Health maintenance
  - Weight reduction if obese
  - Reduce DM risk
  - Reduce CVD risk
  - Reduce Endometrial CA risk
- Patient education and support

PCOS Sample Treatment Plan

Fundamental

- High protein/low carb diet for 60 days, then modified Mediterranean diet; Flax seeds, ground- 1-2 tbsp/day
- Frequent exercise 5x/week (cardio); strength train 2x/week
- Soy powder 30 gm protein/30-90 mg isoflavones
- NAC 600 mg tid
- Black cohosh 40 mg/day 10 days/month (day 2-9)

Top Add ons

- Myoinositol 4 gm/day vs D chiroinositol 1 gm/day
- Nettles root 400 mg/day
- Green tea extract 1-2 caps per day
- Licorice Extract 3.5 gm/day
- Fenugreek 25 gm/day
- Saw palmetto s.e. 85-95% f.a./sterols 160 mg bid

Considerations

- Cyclic OMP 100-200 mg bid x 12 days/month
- Calcium, Chromium, Fish oil, Vitamin D, Berberine
- Pinitol 600 mg bid or PGX granules
- Meds : Metformin 1-2 gm/day, spironolactone, Vaniqa, OCPs (with drosperinone)

Natural Treatment Interventions Hyperprolactinema

- Assure absence of tumor; R/O other causes
- Vitex

Modulates secretion of prolactin from the pituitary gland-animals
Vitex inhibits prolactin release by the pituitary gland-rats
52 women with hyperprolactinemia; given vitex extract 20 mg x 3 mo.
Milewicz. Arzneim-Forsch Drug Res 1993;43

- Consider conventional treatment

(Chasteberry [Vitex])

Vitex and PCOS (Review)[1]

- Evidence for an equivalent effect of pharmaceutical agent bromocriptine and Vitex agnus-castus.
  - 1**. Lowers prolactin due to dopaminergic effects** [38-41,63] – 40 mg daily for 3 months
  - 2. No change for serum prolactin [64*] – 20mg daily for 3 months
  - 3. FSH no change [39] - 40 mg daily for 3 months
  - 4. LH no change [39] - 40 mg daily for 3 months
  - 5. LH lowered [49] – *Animal study*
  - 6. Binds to β estrogen receptors [38,43,69] – 40mg daily for 3 months
  - 7. Increased serum estradiol [49,64] - 20mg daily for 3 months
  - 8**. Increased serum progesterone** [49,62] - 20mg daily for 3 months
  - 9. **Improved pregnancy rates** [61,62**] - 20mg daily for 3 months

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Vitamin B6- Hyperprolactinemia

- Galactorrhea-amenorrhea syndrome and elevated prolactin concentrations experienced a return of regular ovulatory menses within 37-94 days after starting pyridoxine treatment (200-600 mg/day). In each the galactorrhea ceased and serum prolactin levels were maintained in the normal range while taking pyridoxine.
- In the three women effectively treated with pyridoxine, the galactorrhea returned, serum prolactin levels increased, and the menses ceased after discontinuing pyridoxine..

J Clinical Endocrinology & Metabolism, Vol 42, 1192-1195,

Hyperprolactinemia Sample Tx Plan

6 months:

- Chaste tree berry (.6% aucubin) 215 mg/cap
  2 caps daily
- L-tyrosine 500-1500 mg/day
- Vitamin B6 200-600 mg/day

- Calcium/ vitamin D/ trace minerals

Natural Treatment Interventions Hypothalamic Amenorrhea

- **Anorexia nervosa/other eating disorder**
- **Psychotherapy; inpatient/outpatient**

  Constitutional therapy

  Homeopathy

  Nutrition; IV

  Exercise issues

  Morbidity/Mortality issues
- **If Weight loss/underweight**

  Correct cholesterol deficiency

  Malnutrition

  Decrease exercise

Natural Treatment Interventions Hypothalamic Amenorrhea

Botanicals/nutraceuticals

Maca root 2 gm/day

others to consider-Vitex 1 cap standardized extract daily

-Rhodiola 200 mg per day

- Polyglandular support

-Depression -St. Johns wort, SAMe, tyrosine, phenylalanine, D, B12, folic acid, B6, L-tryptophan, 5-HTP

-Anxiety-, lavender, Kava, passiflora, valerian,lemon balm

-Adaptogens-Ginseng, licorice, Rhodiola, Ashwagandha, Maca, Schisandra

Hypogonadotropic Hypogonadism (Hypothalamic Amenorrhea)

3-6 month Sample Tx Plan

- **Address appropriate nutrition issues**
- **ex/ Vegan, drastic diets, eating disorder, low fat, low calories**
  - **Very individualized; ovulation support= flax seeds, soy foods**
- **Address stressors**
- **ex/ psychotherapy, trauma healing**
- **Address depression and/or anxiety**
  - **SJW 300 mg S.E. tid (cons/SAMe, 5-HTP, other A.A.)**
  - **GABA 500 mg tid (cons/Kava, l-theonine, other A.A.)**
- **Polyglandular support**
- **Rhodiola 200-400 mg per day**
- **Maca 2 gm/day**

Hypothalamic Amenorrhea Must consider Hormones

Up To Date

- For restoration of menses and improvement in bone density: increased caloric intake, decreased exercise, or both, along with work to increase body weight if less than 90 percent of ideal body weight

- Behavioral therapy if there is a history of irregular eating behavior or distorted body image and resistance to decreasing exercise and/or weight gain.
- Baseline BMD; then f/u for a year to determine if menses resume before considering estrogen replacement therapy.
- Hormonal therapies: transdermal E2 patches (100 mcg) administered continuously with cyclic micronized progesterone 200 mg for 12 days every month (for endometrial protection

- Bisphosphonates should be avoided in these women, even when bone density is low, unless estrogen replacement therapy is contraindicated or has been demonstrated to be ineffective in preventing fractures. Teriparatide may be an option for patients with FHA who have delayed fracture healing and very low bone density if estrogen replacement therapy is ineffective
- Ovulation induction therapies should not be initiated unless the patient has achieved a healthy weight and understands the need for continued focus on adequate caloric intake

- Complications: estrogen deficiency (osteoporosis, CAD, Dementia, QOL; more rapid aging)

Resources

- Women's Encyclopedia of Natural Medicine, 2008, second edition
- www.drtorihudson.com
- www.awomanstime.com
- www.instituteofwomenshealth.com
- www.naturopathicresidency.org
- DrHudson@awomanstime.com
- www.vitanicapro.com
- Monthly columns
    - Townsend Letter for Doctors
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