

Managing Primary Ovarian Insufficiency

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Disclosure

- Speakers Bureau –Merck
- I have no financial disclosures relative to this material
- Any unlabeled/unapproved uses of drugs or products referenced will be disclosed

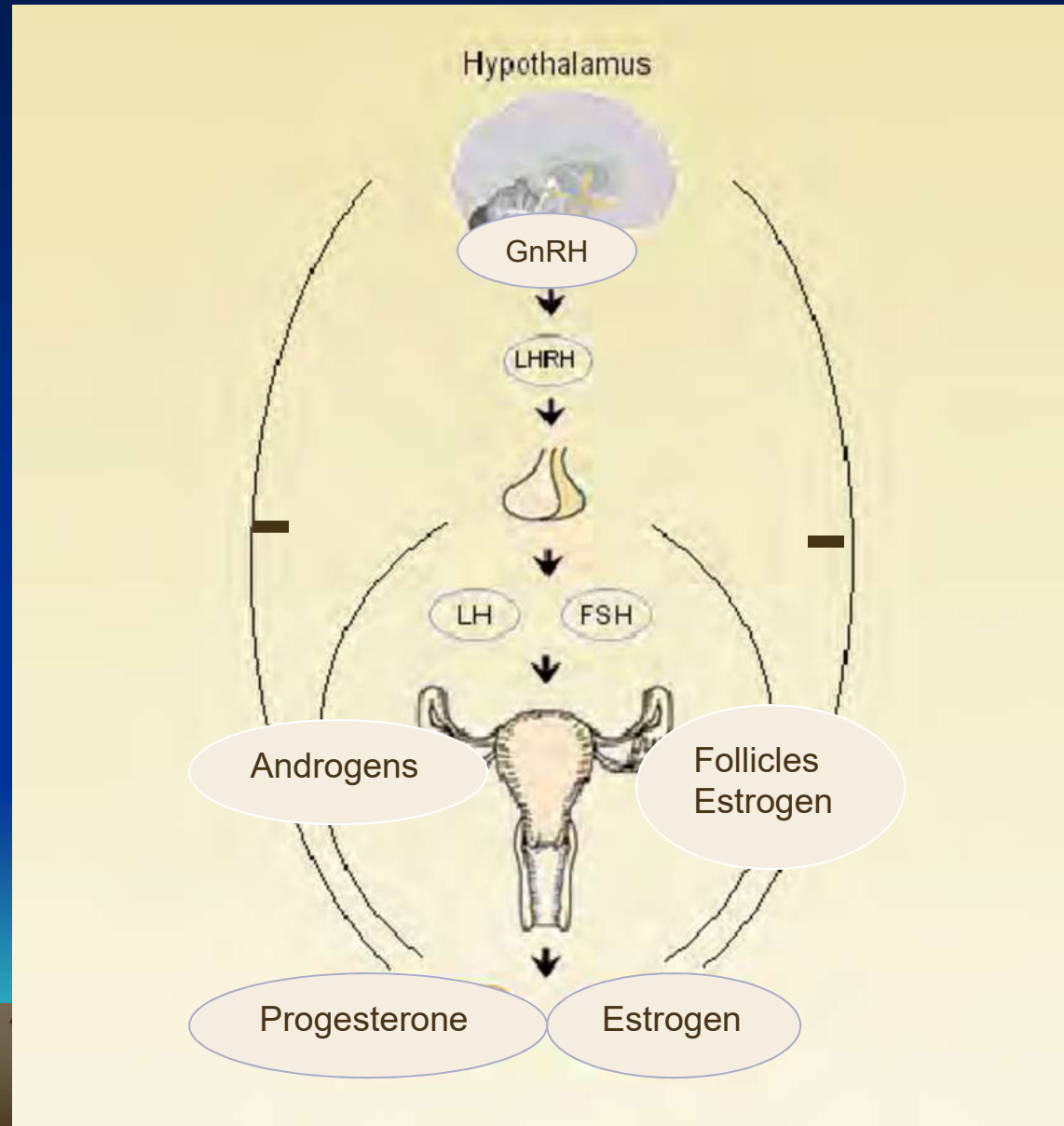
Objectives

- Describe clinical findings leading to a diagnosis of primary ovarian insufficiency
- Identify the most common causes of primary ovarian insufficiency
- Discuss management of primary ovarian insufficiency

Case

- 32-year-old g0 c/o amenorrhea for 8 months. Her periods started when she was 12 and were normal until about 2 years ago. Since then they've been increasingly far apart. She says her weight is stable and she's been feeling well. Her partner is a female so she hasn't been using contraception and knows she isn't pregnant. The only symptoms she's noticed are feeling hot occasionally and waking up a lot at night. Her partner says she's seemed somewhat moody lately.

Causes of Secondary Amenorrhea



Causes of Secondary Amenorrhea

- **Pregnancy**
- Breast-Feeding
- Depressed Hypothalamus
 - Eating disorder
 - Excessive physical training
 - Emotional stress
 - Serious medical conditions

Causes of Secondary Amenorrhea

- Pituitary
 - Hyperprolactinemia
- Thyroid
 - Hypothyroidism or Hyperthyroidism
- Ovarian
 - Primary ovarian insufficiency (POI)
- Uterine
 - Iatrogenic: multiple or vigorous D&Cs (Asherman's Syndrome)

Causes of Secondary Amenorrhea

- Other Hormone Imbalance
 - PCOS (most common cause)
 - Obesity
 - Perimenarche, perimenopause
- Medications
 - Hormones, especially contraceptives
 - Psychotropic drugs
 - Others

Taking the History

- Onset
 - Gradual vs. sudden
 - Perimenarche, perimenopause
- Associated symptoms
 - Breast tenderness, N&V
 - Stress, physical or emotional
 - Weight gain or loss
 - Systemic – fatigue, fever

Taking the History

- Symptoms of endocrinopathy
 - Pituitary
 - Galactorrhea, headache, visual changes
 - Thyroid
 - Nervousness, tremor, palpitations, weight loss
 - Fatigue, cold intolerance, skin changes, weight gain, constipation
 - Androgen Excess – hirsutism, acne
 - POI – menopausal symptoms

Additional Focused History

- Gynecologic history
 - Annual exams, contraception
 - Pregnancies/problems
 - Past pelvic surgeries or problems
- Past Medical History
 - Medical illnesses
 - Surgeries, esp. D&C
 - Medications
- Family History
 - Age at menarche, menopause
 - Menstrual Abnormalities
 - PCOS and POI both run in families

Checklist for Physical Exam

- Low or high BMI
- Enlarged thyroid or thyroid nodule
- Galactorrhea
- Hirsutism or acne (Hyperandrogenism)
- Complete physical/pelvic exam
 - Evaluate **ESTROGEN STATUS**

Estrogen Status

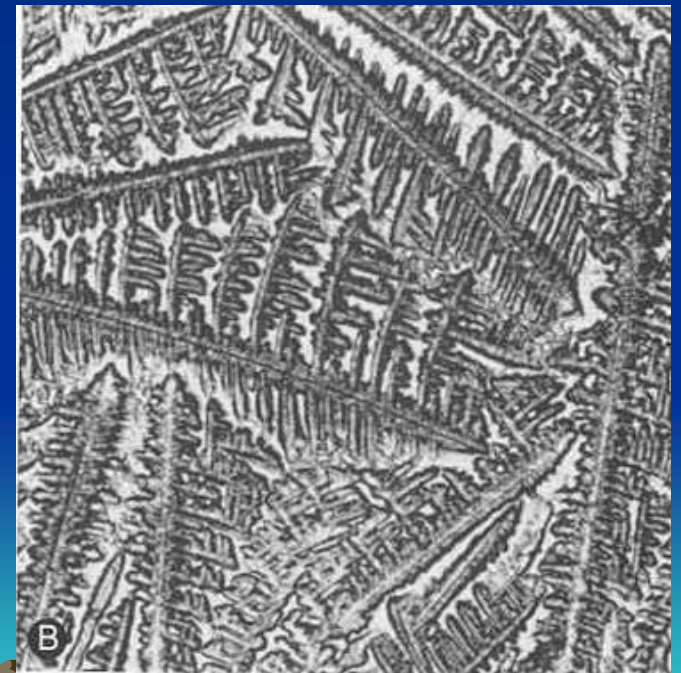
Hypoestrogenized

- Hypothalamic amenorrhea
- Hyperprolactinemia
- Hypothyroidism
- Primary Ovarian Insufficiency
- Menopause

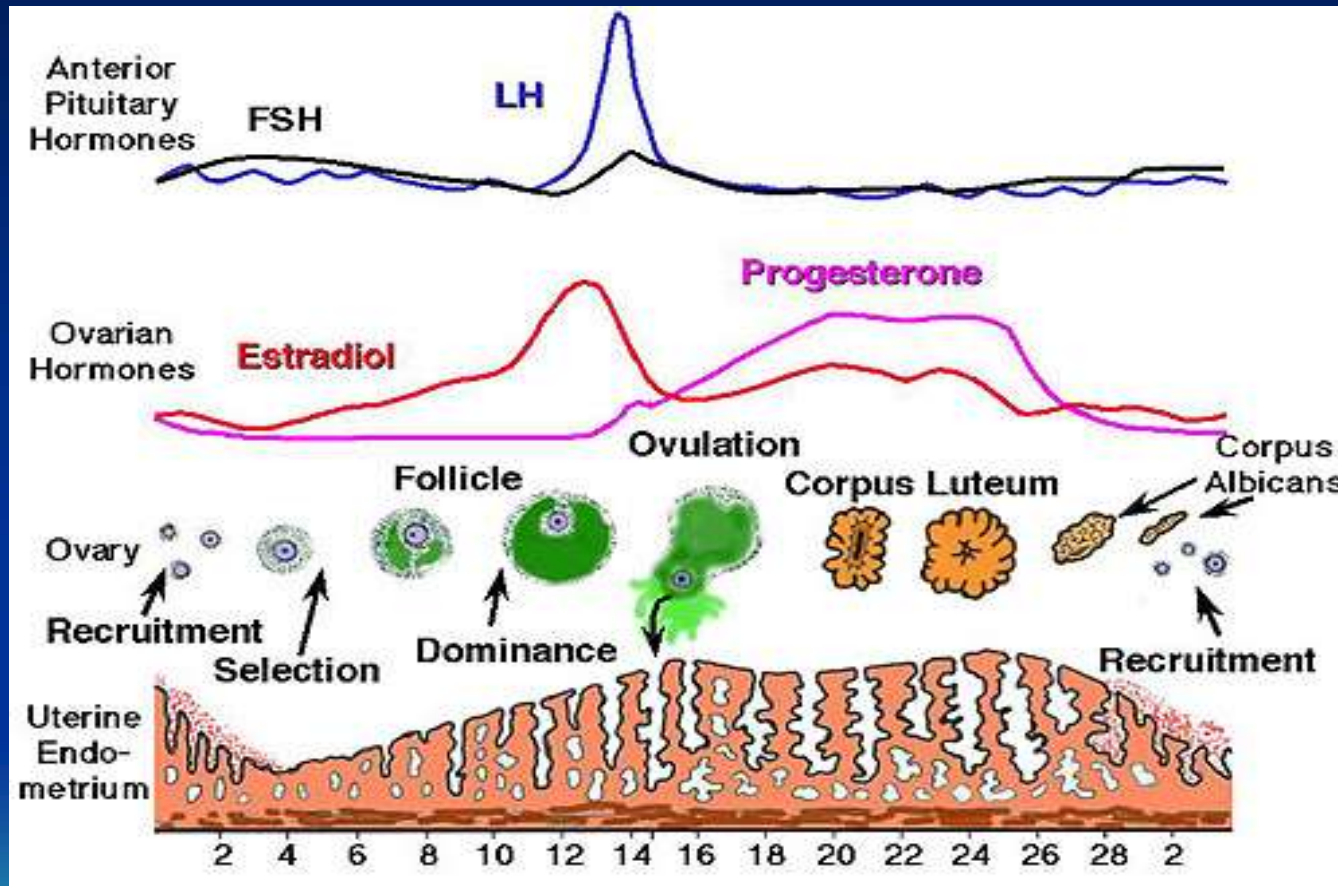
Estrogenized

- PCOS
- Obesity-related amenorrhea

✓ Vaginal Dryness/Epithelium + Estrogenic Cervical Mucous



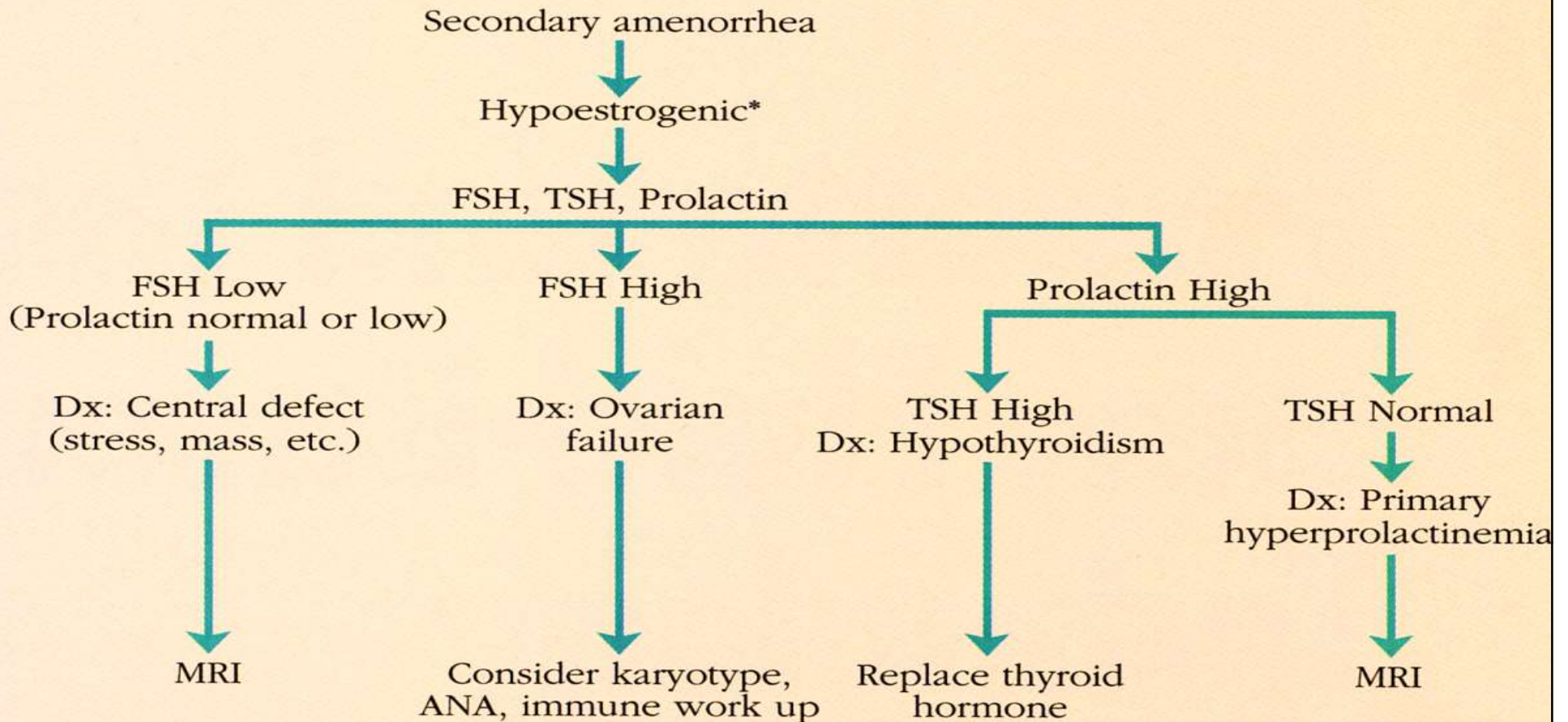
Progestin Challenge Test



Progestin Challenge Test

- If uncertain estrogen status
 - Provera 10 mg x 10 days
 - Low estrogen – minimal or no bleeding
 - Estrogen present – moderate to heavy bleeding
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- Measurement of endometrial thickness by ultrasound may also be helpful

Diagnosis of secondary amenorrhea (hypoestrogenic)



** Based on clinical exam (cervical mucus), office maturation index and, possibly, endometrial thickness.*

Schlaff WD. OBG Mgt. March 1997.

Factoid about TSH and Hyperprolactinemia

- Dopamine = PIF (prolactin inhibiting factor)
- TRH = PRF (prolactin releasing factor)
- With significant hypothyroidism, feedback to hypothalamus causes \uparrow TRH, which is \uparrow PRF, which increases prolactin
- \uparrow TRH also of course increases TSH

Laboratory Evaluation

- Pregnancy Test
- TSH
- Prolactin
- FSH
- If indicated
 - CBC, Chem screen
 - 17OHP, Testosterone, and DHEAS

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- What additional history do we need?
 - No previous medical problems or surgery
 - Her mother had menopause at age 48
 - Denies endocrine symptoms
 - No extraordinary recent stress
- Physical exam
 - BMI 24
 - Normal physical and pelvic exam
 - Vagina somewhat pale, no cervical mucous
- What lab should we order?
 - TSH, prolactin normal
 - FSH 60

Diagnosis: Primary Ovarian Insufficiency

Primary Ovarian Insufficiency

- Definition: Depletion or dysfunction of ovarian follicles with cessation of menses before age 40
- Can be permanent OR intermittent and unpredictable
- Considered a pathologic condition, not a hastening of natural menopause
- 2-10% of patients presenting with amenorrhea (1% of all women) will be diagnosed with POI

ACOG Committee Opinions #605 and 698.

Most Common Symptoms

- Amenorrhea - 100%
- Mood swings - 73%
- Insomnia - 58%
- Sexual problems - 58%
- Fatigue - 57%
- Hot flashes - 47%

Menopause January 2021; E pub.

Etiologies

- Chromosomal abnormalities
 - Turner's syndrome mosaic
 - Fragile X permutation carrier
 - Unknown, but 10-20% have + family history
- Autoimmune disease (20%)
- Others
 - History of chemotherapy or radiation
 - Previous pelvic surgery
 - Infectious or infiltrative disease (rare)
 - Unknown (most common)

Additional Testing

- To establish diagnosis
 - Repeat FSH (>30) with estradiol (<50) in one month
 - Consider Anti-Mullerian Hormone (AMH)
 - Pelvic ultrasound
- To discover etiology
 - Karyotype
 - FMRI gene (for Fragile X permutation)
 - ANA, TSH, Thyroid peroxidase antibodies, Adrenal antibodies

Associated Risks if Autoimmune Etiology

- Autoimmune disorders, esp. endocrine
 - 20% incidence of thyroid disease
 - Adrenal insufficiency, which can lead to Addison's disease
 - Diabetes, lupus, RA, pernicious anemia, etc.

POI Associated Risks

- Basal estrogen levels lead to
 - 35% ↑ incidence of cardiovascular disease
 - ↑ Stroke
 - ↑ Cardiovascular and all-cause mortality
 - Bone loss, osteoporosis
 - Neurocognitive changes, including ↑ Parkinson's
 - Psychiatric problems (depression, anxiety)
 - Urogenital changes associated with sexual dysfunction

JAMA 2019; 322(24):2411-2421..

Management

- Hormone Replacement Therapy (E+P) essential for cardiovascular and bone health and to manage symptoms
 - Estradiol patch (or systemic ring) with P preferred
 - Higher estrogen dose than used for natural menopause (e.g., .1 mg patch, 2 mg estradiol po)
 - Continue until the age of natural menopause (51-52)
- Rarely, HRT can induce ovulation
- (Note: 5-10% of patients may conceive due to “spontaneous remission of POI”)

* Menopause 2020 27:1110-1116

Management

- If pregnancy not desired
 - Oral contraceptives
 - Failures have been reported due to high FSH → avoid ultra-low dose pills
 - May be superior for protecting bone*
 - OR estradiol therapy with LNG IUD
- Calcium (1200-1500 mg) + vitamin D (1000 IU)
- Weight bearing and resistance exercise

* Menopause 2020;27:1110-1116.

Counseling

- Implications for self image
- Importance of long-term hormone therapy
- Fertility issues
 - Effect on patient and partner
 - If fertility desired, pregnancy can be achieved in vitro with donor eggs
- Consider psychologic support, esp. in very young patients

Follow Up

- Regular monitoring of HT
- Annual thyroid screen, including thyroid peroxidase antibodies
- Annual test for adrenal antibodies
 - If + adrenal antibodies, annual corticotropin stimulation test
- Monitor for symptoms of other autoimmune conditions

Resources

- International Premature Ovarian Failure Association at <http://www.ipofa.org>
- Eunice Kennedy Shriver National Institute of Child Health and Early Development. Primary Ovarian Insufficiency. at <http://poi.nihcd.nih.gov>

Surgical Menopause

Surgical Menopause (Removal of ovaries - BSO)

- Abrupt and profound loss of estrogen
- 23% of US women aged 40-44 and 45% of those aged 45-49 undergo BSO
- Sudden and severe onset of menopausal symptoms
- Increased risk for cardiovascular disease, osteoporosis, cognitive decline, anxiety and depression, and all-cause mortality, particularly if occurs before age 45

Obstet Gynecol 2020;135:853-68.

Estrogen Replacement in Surgical Menopause

18-year follow up of WHI estrogen-only arm:

- If BSO done before age 45 and women took ERT - 40% decrease in all-cause mortality vs. placebo
- If BSO done before menopause and women took ERT - 32% reduction in all-cause mortality
- Safe to continue ERT until age 60 and begin ERT any time before age 70

Ann Intern Med 2019;171:406-414.

Sexual Concerns

- Always obtain a sexual history on these patients
- Both women with POI and women post BSO likely to experience genitourinary syndrome of menopause
 - Can be relieved with systemic estrogen, but may require local therapy as well
- Women post BSO also have significant ↓ testosterone, which often leads to hypoactive sexual desire disorder
 - Prescribe testosterone therapy as needed

Obstet Gynecol 2020;135:853-68.

Conclusions

- Both POI and surgical menopause result in significant health risks and negative effects on quality of life secondary to decreased estrogen production
- Hormone Therapy is vital to mitigating the health risks and improving quality of life
- Concerns about HT raised by the WHI do not apply to these populations!