INTRODUCTION

• Normal women have menopause at a mean age of 51 years, with 95 percent becoming menopausal between the ages of 45 to 55 years.

• The resulting lack of estrogen is associated with rapid bone loss due to increased bone resorption and often consequent osteoporosis.

• Many women also experience menopausal symptoms, including hot flashes, vaginal dryness, and urinary symptoms.

• Can be relieved with hormones.
INTRODUCTION

• 75% OF PERIMENOPAUSAL WOMEN IN THE UNITED STATES HAVE HOT FLASHES.

• A SYSTEMATIC REVIEW OF 66 STUDIES REVEALED THAT HOT FLASHES ARE REPORTED BY 41.5% OF POSTMENOPAUSAL WOMEN WORLDWIDE.
INTRODUCTION

% of women 40-55

AA Hispanic Caucasion Asian

US dept of health and human services. Administration on aging 2000
WHY MENOPAUSE
INTRODUCTION

• IN 2001, THE STAGES OF REPRODUCTIVE AGING WORKSHOP (STRAW) ESTABLISHED A NOMENCLATURE AND A STAGING SYSTEM THAT HAS SINCE BEEN WIDELY ADOPTED AS THE GOLD STANDARD.
<table>
<thead>
<tr>
<th>Stage</th>
<th>-5</th>
<th>-4</th>
<th>-3b</th>
<th>-3a</th>
<th>-2</th>
<th>-1</th>
<th>+1a</th>
<th>+1b</th>
<th>+1c</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology</td>
<td><strong>REPRODUCTIVE</strong></td>
<td><strong>MENOPAUSAL TRANSITION</strong></td>
<td><strong>POSTMENOPAUSE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
<td>Early</td>
<td>Late</td>
<td>Early</td>
<td>Late</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>variable</td>
<td>variable</td>
<td>1-3 years</td>
<td>2 years (1+1)</td>
<td>3-6 years</td>
<td>Remaining lifespan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PRINCIPAL CRITERIA**

<table>
<thead>
<tr>
<th>Menstrual Cycle</th>
<th>Variable to regular</th>
<th>Regular</th>
<th>Regular</th>
<th>Subtle changes in Flow/Length</th>
<th>Variable Length Persistent ≥7- day difference in length of consecutive cycles</th>
<th>Interval of amenorrhea of ≥60 days</th>
</tr>
</thead>
</table>

**SUPPORTIVE CRITERIA**

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>FSH</th>
<th>AMH</th>
<th>Inhibin B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Variable* Low</td>
<td>Variable* Low</td>
<td>↑ Variable Low</td>
</tr>
<tr>
<td>↑ ≥25 IU/L** Low</td>
<td>Stabilizes Very Low</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Antral Follicle Count | Low | Low | Low | Low | Very Low | Very Low |

**DESCRIPTIVE CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor symptoms</td>
<td>Likely</td>
<td></td>
</tr>
<tr>
<td>Vasomotor symptoms</td>
<td>Most Likely</td>
<td></td>
</tr>
<tr>
<td>Increasing symptoms of urogenital atrophy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Blood draw on cycle days 2-5  ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard

Soules Menopause 2001
LATE REPRODUCTIVE STRAW STAGES -3B TO -3A

- **-3B:**
  - NORMAL CYCLES AND FSH
  - LOW AMH, ANTRAL FOLLICLE COUNT (AFC) AND INHIBIN

- **-3A:**
  - SHORTER CYCLES (BY 2-3 DAYS)
  - HIGHER FSH
  - LOW AMH, AFC, INHIBIN
MENOPAUSE TRANSITION STRAW STAGES -2 TO -1

• IRREGULAR CYCLES, INCONSISTENT OVULATION

• EARLY STAGE -2
  • PERSISTENT SHORTENING (VARIABLE BY 7 DAYS FOR PAST AT LEAST 10 MENSES)
  • AMH, AFC, INHIBIN CONTINUE TO DECLINE, WHILE FSH INCREASES
  • ESTRADIOL ELEVATED WHILE PROGESTERONE LOWER IN LUTEAL PHASE

• LATE STAGE -1
  • EPISODES OF AT LEAST 60 CONSECUTIVE DAYS OF AMENORRHEA
  • FSH>25IU/L
  • LASTS 1-3 YEARS AND CHARACTERIZED BY HOT FLASHES
• HORMONE REPLACEMENT THERAPY (HRT) IS EXTENSIVELY USED IN THE UNITED STATES, ESPECIALLY FOR:
  • TREATMENT OF MENOPAUSAL SYMPTOMS
  • PREVENTION OF HEART DISEASE
  • PREVENTION AND TREATMENT OF OSTEOPOROSIS
• Typically women are treated for 5 years.

• Prior to the WHI women were routinely prescribed long term HRT for cardio and bone protection based on observational data.

• There is no strong evidence that HRT is cardioprotective especially if menopause was remote (>5-10 years).

• WHI showed the opposite.
• THERE IS SOME EVIDENCE (BUT NOT CONCLUSIVE) FOR USING HRT FOR:
  • PREVENTION OF COLON CANCER
  • PREVENTION OF DEMENTIA
WHI

• WHI (WOMEN’S HEALTH INITIATIVE)

• SUBJECTS: >160,000 MULTI-ETHNIC WOMEN AGED 50-79YO (MEAN 63); >27,000 ON HRT FOR 6-11 YEARS

• DOUBLE-BLIND

• CLINICAL TRIAL (64,500 WOMEN) AND OBSERVATIONAL STUDY (100,000 WOMEN)

• OBJECTIVE: TO EVALUATE STRATEGIES FOR PREVENTING CAD, BREAST CANCER, COLON CANCER, AND OSTEOPOROSIS
WHI

- The benefits of combined HRT appear to outweigh its risks for most symptomatic women who are either under age 60 years or less than 10 years from menopause who do not have contraindications:
  - History of breast cancer
  - Coronary heart disease
  - Previous venous thromboembolic event or stroke
  - Active liver disease
WHI

<table>
<thead>
<tr>
<th></th>
<th>CEE/MPA (n=8506)</th>
<th>Placebo (n=8502)</th>
<th>Difference per 10000 wyrs</th>
<th>HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular incidents</td>
<td>196</td>
<td>159</td>
<td>6</td>
<td>1.18 (0.95-1.45)</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>206</td>
<td>155</td>
<td>9</td>
<td>1.24 (1.1-1.53)</td>
</tr>
</tbody>
</table>
DECREASED RISK OF COLORECTAL CANCER

• IN THE WHI STUDY, COMBINED HRT WAS ASSOCIATED WITH A SIGNIFICANT REDUCTION IN THE CUMULATIVE HAZARD OF INVASIVE COLORECTAL CANCER (HAZARD RATIO 0.56, 95 PERCENT CI 0.38 TO 0.81).
DECREASED RISK OF HIP FRACTURE

• COMBINED HRT WAS ASSOCIATED WITH SIGNIFICANT REDUCTION IN HIP FRACTURE (5 FEWER HIP FRACTURES PER 10,000 PERSON-YEARS; HR 0.7, UNADJUSTED 95% CI 0.4-1.0).
ESTROGEN DECREASES RISK OF UTI

- ESTROGEN THERAPY (INTRAVAGINAL ESTRIOL) WAS ASSOCIATED WITH A MUCH GREATER LIKELIHOOD OF REMAINING FREE OF UTI AS COMPARED TO PLACEBO.
TRANSDERMAL AND ORAL ESTROGEN PREVENT BONE LOSS

Stevenson JC Lancet 1990
HRT AND RISK OF THROMBO-EMBOLISM

- ABSOLUTE RISK INCREASES WITH AGE
- GENERAL POPULATION
  - ~50/100,000 PER YEAR FOR WOMEN IN 40S
  - ~ 90/100,00 PER YEAR IN 50S/60S
  - ~ 350/100,000 PER YEAR IN 70-80
  - 700/100,000 PER YEAR ABOVE AGE 80

Canonico 2007
Battaglioli 2007
Cassanova 2012
HRT AND RISK OF THROMBO-EMBOLISM

• RR 2-5X GREATER WHEN TAKING HRT
• WHI SHOWED AN INCREASE OF 41% IN NONFATAL STROKES
• RISK EVEN GREATER IF HAS OTHER RISKS LIKE OBESITY, IMMobilIZATION AND FRACTURE
• NATURAL PROGESTERONE NOT ASSOCIATED WITH INCREASED RISK
• SYNTHETIC PROGESTINS CAN INCREASE THE RISK

Canonico 2007
Battaglioli 2007
Cassanova 2012
HRT AND RISK OF THROMBO-EMBOLISM

- Risk is lower if the HRT is transdermal
- This is due to the avoidance of first pass effect on the liver
- OR for oral = 4.2 (95% CI 1.5-11.6) vs transdermal OR = 0.9 (95% CI 0.4-2.1) compared to non estrogen users
- This was confirmed by other studies
- Same with vaginal route (Ring)

Scarabin Lancet 2003
Renoux BMJ 2010
Minkin J Reprod Med 2004
HRT AND HEART DISEASE

• OLDER DATA FROM OBSERVATIONAL STUDIES SHOWED THAT HRT WAS CARDIOPROTECTIVE.

Barrett-Connor 1991
Grady 1992
Barrett-Connor 1998
Grodstein 2000
Psaty 1994
Sidney 1997
Stampfer 1991
Stampfer 1985
HRT AND HEART DISEASE

• CONFLICTING DATA CAME FROM WHI AND HERS TRIALS

• MORE RECENT TRIALS SHOWED THAT IF ADMINISTERED NEAR MENOPAUSE (<10YRS FROM MENOPAUSE OR <60 YEARS OF AGE) MAY HAVE PROTECTIVE BENEFIT

• WHI SHOWED AN INCREASE OF 29% IN CARDIAC EVENTS

Barrett-Connor 2007
Manson 2007
Hsia 2006
HRT AND HEART DISEASE

- WOMEN WITH KNOWN CHD WHO TOOK HRT HAD A 52% INCREASE IN CHD EVENTS
- ERT ARM OF THE WHI SHOWED NO INCREASE IN CHD COMPARED TO PLACEBO BUT NO PROTECTION WITH INCREASE IN STROKES
- SUBANALYSIS OF WHI SHOWED IMPROVED LIPID, GLUCOSE AND INSULIN PROFILES WITH HRT COMPARED TO PLACEBO

Barrett-Connor 2007
Manson 2007
Manson 2003
Hsia 2006
HRT AND HEART DISEASE

- HERS (HEART AND ESTROGEN REPLACEMENT STUDY)
- 2763 POSTMENOPAUSAL WOMEN WITH KNOWN CHD, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED SECONDARY PREVENTION TRIAL
- RESULTS: DECREASE LDL, INCREASE HDL, INCREASE TG’S, NO CHANGE IN CARDIAC EVENTS
HRT AND HEART DISEASE

• CAD (ESTROGEN REPLACEMENT AND CORONARY ARTERY DISEASE) TRIAL
• 10 YEAR RANDOMIZED ANGIOGRAPHIC STUDY
• 2268 WOMEN WITH CAD, RANDOMIZED TO TREATMENT VS PLACEBO
• RESULTS SHOWED A STATISTICALLY SIGNIFICANT (P <0.007) IMPROVEMENT IN SURVIVAL FOR WOMEN ON HRT
HRT AND HEART DISEASE

• ACAPS (ASYMPTOMATIC CAROTID ATHEROSCLEROTIC PROGRESSION STUDY)
• POSTMENOPAUSAL WOMEN WITH ASYMPTOMATIC CAROTID DISEASE
• RESULTS SHOWED CESSATION OF PROGRESSION AND SOME REGRESSION OF CAROTID ARTERY ATHEROSCLEROSIS AS ASSESSED BY ULTRASOUND
HRT AND HEART DISEASE

• PEPI TRIAL (POSTMENOPAUSAL ESTROGEN AND PROGESTERONE INTERVENTIONS)
• 875 POSTMENOPAUSAL WOMEN, BLINDED PLACEBO CONTROLLED
• RESULTS: INCREASE IN HDL, INCREASE IN TRIGLYCERIDES
• ERA (ESTROGEN REPLACEMENT AND ATHEROSCLEROSIS) TRIAL

• 309 POSTMENOPAUSAL WOMEN WITH KNOWN CAD, RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROL TRIAL (3 YEAR FOLLOW-UP)

• OBJECTIVE: TO DETERMINE EFFECTS OF HRT VS. PLACEBO ON PROGRESSION OF ATHEROSCLEROSIS (USING ANGIOGRAPHY)

• RESULTS: IMPROVED LIPID PROFILE, BUT DID NOT ALTER PROGRESSION OF ATHEROSCLEROSIS
HRT AND HEART DISEASE

• ONGOING STUDIES KRONOS AND THE EARLY VS LATE INTERVENTION TRIALS
HRT AND BREAST CANCER

• RISK OF BREAST CANCER IS 1/8

• THE ABSOLUTE INCREASE IN RISK WHEN TAKING COMBINATION HRT IN THE WHI WAS 8 MORE CANCERS PER 10,000 WOMEN YEARS AND 2 ADDITIONAL DEATHS DUE TO BREAST CANCER PER 10,000 WOMEN YEARS.
HRT AND BREAST CANCER

• OBSERVATIONAL STUDY OF THE WHI AND OTHERS REPORTED THAT INITIATION OF HRT SOON AFTER MENOPAUSE WAS ASSOCIATED WITH INCREASED BREAST CANCER RISK (HR=2.75)
NATURAL OCCURRING ESTROGENS ARE ESTRONE (E1), 17 B ESTRADIOL (E2) AND ESTRIOL (E3)

ACTIVITY E2 > E1 (50-70%) > E3 (90% LESS)
NONHUMAN ESTROGENS

• CONJUGATED ESTROGENS
  • COMBINATION OF AT LEAST 10 COMPOUNDS
  • FROM CONCENTRATION OF PREGNANT MARES
SYNTHETIC ESTROGENS

• ESTERIFIED ESTROGENS SUCH AS ESTRONE SULFATE OR SYNTHETIC CONJUGATED ESTROGENS
• SYNTHETIC ESTROGEN ANALOGS SUCH AS ETHINYL ESTRADIOL AND ESTRIPOPIATE
PLANT BASED ESTROGENS (PHYTOESTROGENS)

• ISOFLAVONES DO NOT HAVE THE STEROID CHEMICAL SKELETON BUT HAVE ESTROGENIC EFFECT ON SOME TISSUES WHILE ANTIESTROGENIC ON OTHERS
ESTROGEN PREPARATIONS

• ORAL
• TRANSDERMAL
• TOPICAL GELS
• EMULSIONS AND LOTIONS
• INTRAVAGINAL CREAMS AND TABLETS, AND VAGINAL RINGS.
• IN SOME COUNTRIES, ESTROGEN CAN ALSO BE GIVEN AS A SUBCUTANEOUS IMPLANT
• ALL FDA APPROVED ESTROGEN PRODUCTS ARE EFFECTIVE FOR TREATMENT OF VASOMOTOR SYMPTOMS
• ALL APPROVED VAGINAL CREAMS ARE EFFECTIVE IN TREATING VULVOVAGINAL ATROPHY
• ONLY FEMRING IS APPROVED FOR VASOMOTOR SYMPTOMS AS A VAGINAL PREP
• PREMARIN CREAM AND ESTRING ARE APPROVED FOR DYSPAREUNIA
• ESTRING IS APPROVED URINARY URGENCY AND DYSURIA
ESTROGEN PREPARATIONS

• WOMEN BEING TREATED FOR MENOPAUSAL SYMPTOMS SUCH AS HOT FLASHES REQUIRE SYSTEMIC ESTROGEN

• WOMEN BEING TREATED ONLY FOR VULVOVAGINAL ATROPHY (AKA GENITOURINARY SYNDROME OF MENOPAUSE [GSM]) SHOULD BE TREATED WITH LOW-DOSE VAGINAL ESTROGEN RATHER THAN SYSTEMIC ESTROGEN
ESTROGEN PREPARATIONS

• ORAL ROUTE HAS FIRST PASS EFFECT ON THE LIVER WHICH INCREASES HEPATIC PRODUCTION OF THYROXINE-BINDING GLOBULIN (TBG), CORTICOSTEROID-BINDING GLOBULIN (CBG), SEX HORMONE-BINDING GLOBULIN (SHBG), TRIGLYCERIDES, HIGH-DENSITY LIPOPROTEIN (HDL) CHOLESTEROL, AND CLOTTING FACTORS

• THIS EFFECT IS MINIMALLY INCREASED BY TRANSDERMAL ESTROGEN ADMINISTRATION
### Oral Products

<table>
<thead>
<tr>
<th>Composition</th>
<th>Product name(s)</th>
<th>Range of available dose strengths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated estrogens</td>
<td>Premarin</td>
<td>0.3-1.25 mg</td>
</tr>
<tr>
<td>Synthetic conjugated estrogens, A</td>
<td>Cenestin</td>
<td>0.3-1.25 mg</td>
</tr>
<tr>
<td>Synthetic conjugated estrogens, B</td>
<td>Enjuvia</td>
<td>0.3-1.25 mg</td>
</tr>
<tr>
<td>Esterified estrogens</td>
<td>Menest</td>
<td>0.3-1.25 mg</td>
</tr>
<tr>
<td>17β-estradiol</td>
<td>Estrace, various generics</td>
<td></td>
</tr>
<tr>
<td>Estradiol acetate</td>
<td>Femtrace</td>
<td>0.45-1.8 mg</td>
</tr>
<tr>
<td>Estropipate</td>
<td>Ortho-Est</td>
<td>0.625 mg (0.75 mg estropipate, calculated as sodium estrone sulfate)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.625 mg to 5.0 mg (6.0 mg)</td>
</tr>
</tbody>
</table>

### Transdermal products

<table>
<thead>
<tr>
<th>Composition</th>
<th>Product name(s)</th>
<th>Dose details</th>
</tr>
</thead>
<tbody>
<tr>
<td>17β-estradiol matrix patch</td>
<td>Alora, Climara, Esclim, Fempatch, Menostar, Vivelle, Vivelle-Dot, various generics</td>
<td>0.014-0.1 mg delivered daily, applied once or twice weekly</td>
</tr>
<tr>
<td>17β-estradiol reservoir patch</td>
<td>Estraderm</td>
<td>0.05-0.1 mg delivered daily; applied twice weekly</td>
</tr>
<tr>
<td>17β-estradiol transdermal gel</td>
<td>EstrOgel, Elestrin, Divigel</td>
<td>Applied daily via metered pump or packet delivering 0.52-0.75 mg of 17β-estradiol in gel</td>
</tr>
<tr>
<td>17β-estradiol topical emulsion</td>
<td>Estrasorb</td>
<td>2 packets applied daily</td>
</tr>
<tr>
<td>17β-estradiol transdermal spray</td>
<td>Evamist</td>
<td>1 spray/d, up to 2-3/d if needed</td>
</tr>
</tbody>
</table>

### Vaginal products

<table>
<thead>
<tr>
<th>Composition</th>
<th>Product name(s)</th>
<th>Dose details</th>
</tr>
</thead>
<tbody>
<tr>
<td>17β-estradiol vaginal cream*</td>
<td>Estrace Vaginal Cream</td>
<td>Initially 2-4 g/d for 1-2 wk, followed by maintenance dose of 1 g/d (0.1 mg active ingredient/g)</td>
</tr>
<tr>
<td>Conjugated estrogens cream*</td>
<td>Premarin Vaginal Cream</td>
<td>For vaginal atrophy: 0.5-2 g/d for 21 days then off 7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For dyspareunia: 0.5 g/d for 21 days then off 7 days, or twice weekly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.825 mg active ingredient/g)</td>
</tr>
<tr>
<td>17β-estradiol vaginal ring</td>
<td>Estring</td>
<td>Device containing 2 mg releases 7.5 µg/d for 90 days (for vulvovaginal atrophy)</td>
</tr>
<tr>
<td>Estradiol acetate vaginal ring</td>
<td>Femring</td>
<td>Device containing 12.4 mg or 24.8 mg estradiol acetate releases 0.05 mg/d or 0.10 mg/d estradiol for 90 days (both doses release systemic levels for treatment of vulvovaginal atrophy and vasomotor symptoms)</td>
</tr>
<tr>
<td>Estradiol hemihydrate vaginal tablet</td>
<td>Vagifem</td>
<td>Initially 1 tablet/d for 2 wk, followed by 1 tablet twice weekly (tablet 10 µg of estradiol hemihydrates, equivalent to 10 µg of estradiol; for vulvovaginal atrophy)</td>
</tr>
</tbody>
</table>
TIBOLONE

- Widely used in Europe and other countries for many years for hot flashes, is a synthetic steroid whose metabolites have estrogenic, androgenic, and progestogenic properties.
- Not currently available in the United States.
- It has been shown to reduce vasomotor symptoms and improve BMD.
- Limited data suggest that it may also have a modest effect for symptoms of sexual dysfunction.
TIBOLONE

• IT DOES NOT INCREASE THE RISK OF ABNORMAL MAMMOGRAM OR DENSITY.

• CONFLICTING EVIDENCE OF EFFECT ON BREAST CANCER RISK. IT MAY INCREASE RISK OF RECURRENCE.

• AFTER A MEAN FOLLOW-UP OF THREE YEARS, 237 OF 1556 WOMEN ON TIBOLONE (15%) HAD A BREAST CANCER RECURRENCE, COMPARED WITH 138 OF 1213 (11.4%) IN THE PLACEBO GROUP (HAZARD RATIO 1.40, 95% CI 1.16-1.79).

• THE USE OF TIBOLONE IS CONTRAINDICATED IN WOMEN WITH A HISTORY OF BREAST CANCER.

Kenemans P, Lancet Oncol 2009
TIBOLONE

• CONFLICTING EVIDENCE OF INCREASED RISK OF ENDOMETRIAL HYPERPLASIA.

• HAS A BETTER BLEEDING PROFILE AND IS ASSOCIATED WITH FEWER INCIDENCES OF VAGINAL BLEEDING AS COMPARED TO HRT.

Archer DF, J Clin Endocrinol Metab 2007
ANDROGENS

• EXOGENOUS TESTOSTERONE THERAPY HAS BEEN SHOWN TO IMPROVE SOME ASPECTS OF FEMALE SEXUAL FUNCTION IN CAREFULLY SELECTED POPULATIONS OF POSTMENOPAUSAL WOMEN (EG, THOSE WHO DEVELOP FEMALE SEXUAL INTEREST/AROUSAL DISORDER AFTER UNDERGOING BILATERAL OOPHORECTOMY).

• TESTOSTERONE DOES NOT APPEAR TO HAVE ANY BENEFICIAL EFFECTS ON BONE DENSITY, MOOD, COGNITION, OR VASOMOTOR SYMPTOMS.

• TESTOSTERONE PREPARATIONS IN DOSES APPROPRIATE FOR WOMEN HAVE NOT BEEN APPROVED IN MOST COUNTRIES.
<table>
<thead>
<tr>
<th>US trade name</th>
<th>Progestin (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depo-Provera intramuscular (Pfizer)</td>
<td>Medroxyprogesterone acetate (150 mg/mL)</td>
</tr>
<tr>
<td>Depo-SubQ Provera 104 subcutaneous (Pfizer)</td>
<td>Medroxyprogesterone acetate (104 mg/0.65 mL)</td>
</tr>
<tr>
<td>Liletta 52 mg intrauterine device (Actavis)</td>
<td>Levonorgestrel (releases 0.0186 mg/day, decreasing to approximately 0.0163 mg/day at 1 year, then decreasing to approximately 0.0143 mg/day at 2 years, and 0.0126 mg/day at 3 years)</td>
</tr>
<tr>
<td>Mirena 52 mg intrauterine device (Bayer)</td>
<td>Levonorgestrel (releases approximately 0.02 mg/day, decreasing progressively to 0.01 mg/day by 5 years)</td>
</tr>
<tr>
<td>Skyla 13.5 mg intrauterine device (Bayer)</td>
<td>Levonorgestrel (releases 0.014 mg/day, decreasing to approximately 0.01 mg/day after 60 days, then decreasing to approximately 0.005 mg/day after 3 years)</td>
</tr>
<tr>
<td>Nexplanon 68 mg subdermal implant (Organon)</td>
<td>Etonogestrel (releases 0.06 to 0.07 mg/day in weeks 5 to 6, decreasing to approximately 0.035 to 0.045 mg/day by 1 year, then decreasing to approximately 0.03 to 0.04 mg/day by year 2, and then to 0.025 to 0.03 mg/day by end of year 3)</td>
</tr>
</tbody>
</table>
BIO-IDENTICAL

- Plant derived similar in structure and activity to natural occurring hormones
- FDA regulated micronized progesterone and estradiol
- Non FDA pharmaceutical compounded
- Many pharmacies use the term bio-identical to imply that they are naturally derived (marketing)
- Examples of compounded
  - BIEST (20% E2 and 80% E3)
  - TRIEST (10% E2, 10% E1 and 80% E3)
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage/Regimen</th>
<th>Evidence of Benefit*</th>
<th>FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormonal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen-alone or combined with progestin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Standard Dose</td>
<td>Conjugated estrogen 0.625 mg/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Micronized estradiol-17β 1 mg/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Transdermal estradiol-17β 0.0375–0.05 mg/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>• Low Dose</td>
<td>Conjugated estrogen 0.3–0.45 mg/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Micronized estradiol-17β 0.5 mg/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Transdermal estradiol-17β 0.025 mg/d</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>• Ultra-Low Dose</td>
<td>Micronized estradiol-17β 0.25 mg/d</td>
<td>Mixed</td>
<td>No</td>
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<td>Transdermal estradiol-17β 0.014 mg/d</td>
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<tr>
<td>Estrogen combined with estrogen agonist/antagonist</td>
<td>Conjugated estrogen 0.45 mg/d and bazedoxifene 20 mg/d</td>
<td>Yes</td>
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<tr>
<td>Progestin</td>
<td>Depot medroxyprogesterone acetate</td>
<td>Yes</td>
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<tr>
<td>Testosterone</td>
<td></td>
<td>No</td>
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<tr>
<td>Tibolone</td>
<td>2.5 mg/d</td>
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<tr>
<td>Compounded bioidentical hormones</td>
<td></td>
<td>No</td>
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</table>
ALTERNATIVES TO HRT

• SSRI (RELIEF OF HOT FLASHES USUALLY SEEN WITHIN COUPLE WEEKS WHEREAS EFFECT ON DEPRESSION MAY NEED 6-8 WEEKS)
• SNRI (DESVENLAFAXIN OR PRESTIQ)
• GABAPENTIN (NEURONTIN)
• ESZOPICLONE (LUNESTA) USED FOR NIGHT TIME BUT NOT DAY TIME HOT FLASHES
• PREGABALIN (LYRICA)
• CLINIDIN (CATAPRES)
ALTERNATIVES TO HRT

• COMPLIMENTARY AND ALTERNATIVE MEDICINE (CAM)
  • TRADITIONAL CHINESE MIND BODY/ACUPUNCTURE
  • SOY ISOFLAVONES (HOT FLASHES)
  • BLACK COHOSH (HOT FLASHES)
  • ST JOHNS WORT (MOOD AND ANXIETY)
  • CRANBERRY (UTI)
  • VALERIAN (SLEEP ISSUES IN MENOPAUSE)
  • VITEX (PERIMENPAUSAL UTERINE BLEEDING ABNORMALITY)
ALTERNATIVES TO HRT

• LIFESTYLE MODIFICATIONS
  • DRESS IN LAYERS, DRINK COLD DRINKS, USE FANS, KEEP ROOM COLD AT NIGHT
  • KEEP NORMAL BMI (HIGHER BMI THE MORE FREQUENT HOT FLASHES)
  • STOP SMOKING (SMOKING ASSOCIATED WITH HOT FLASHES)
  • EXERCISE REGULARLY (DAILY EXERCISE ASSOCIATED WITH LESS HOT FLASHES)
  • RELAXATION TECHNIQUES (DEEP BREATHING)
  • AVOID PERCEIVED TRIGGERS (HOT DRINKS, SPICY FOODS, CAFFEINE, EMOTIONAL SITUATIONS)
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage/Regimen</th>
<th>Evidence of Benefit*</th>
<th>FDA Approved</th>
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<tr>
<td><strong>Nonhormonal</strong></td>
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<td>SSRIs and SSNRLs</td>
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<td>Paroxetine</td>
<td>7.5 mg/d</td>
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<td>Stellate-ganglion block</td>
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• HTTPS://WWW.YOUTUBE.COM/WATCH?V=NDFBFXV3JJS&LIST=PLJF-BZI6NAMTXD-TVWBWM3WOKWPJA-CI
CONCLUSION

- Menopause is an opportunity to discuss overall health of the patient including lifestyle.
- HRT is appropriate after considering all the risks and benefits.
- Goal of the therapy should be considered.