

Review of Women's Health

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+ Objectives

- Discuss the World Health Organization's and Center for Disease Control Medical Eligibility Criteria for Contraceptives for 2010
- Review safety and efficacy of hormonal contraceptives in select patient populations
- Evaluate the risk of venous thromboembolism with oral contraceptives
- Discuss the new contraceptive recently approved by the FDA
- Review new dosing of emergency contraception
- Review over-the-counter medications for common ailments during pregnancy and lactation
- Discuss resources available for medication use during pregnancy and lactation
- Review the role of hormone replacement therapy in menopausal women
- Discuss safety data of hormone replacement therapy since the Women's Health Initiative trial



Contraception

+ Hormonal Contraception

- First hormonal contraception
- Amounts of hormones in early combined oral contraceptives (COC) versus current amounts

Pop Quiz:
How much estrogen was in the first combined oral contraceptive that came to market?

+ Contraception Statistics

- Use of Contraception in the United States: 1982-2008 from the National Center for Health Statistics, a division of the Centers for Disease Control and Prevention¹
 - Half of all pregnancies are unintended
 - More than 99% of women 15-44 years of age have used at least one contraceptive method
 - Oral contraceptive pills are used by 17.3% or 10.7 million women
 - Female Sterilization - 16.7% or 10.3 million women

+ Conditions associated with increased risk for adverse health events as a result of unintended pregnancy²

- Breast cancer
- Complicated valvular heart disease
- Diabetes: insulin-dependent; with nephropathy/retinopathy/neuropathy or other vascular disease; or of >20 years' duration
- Endometrial or ovarian cancer
- Epilepsy
- Hypertension (systolic >160 mm Hg or diastolic >100 mm Hg)
- History of bariatric surgery within the past 2 years
- HIV/AIDS
- Ischemic heart disease
- Malignant gestational trophoblastic disease
- Malignant liver tumors (hepatoma) and hepatocellular carcinoma of the liver
- Peripartum cardiomyopathy
- Schistosomiasis with fibrosis of the liver
- Severe (decompensated) cirrhosis
- Sickle cell disease
- Solid organ transplantation within the past 2 years
- Stroke
- Systemic lupus erythematosus
- Thrombogenic mutations
- Tuberculosis

+ CDC Medical Eligibility Criteria²

- http://www.cdc.gov/mmwr/preview/mmwrhtml/rr59e0528a1.htm?s_cid=
- Created from guidance developed by the World Health Organization
- Updates will typically occur every 3-4 years
- Updates will appear on the CDC U.S. MEC website
 - <http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/USMEC.htm>

+ Recommendations for Use of Contraceptive Methods

- Provides guidance for the following contraceptive options:
 - Combined hormonal contraceptive methods including low-dose combined oral contraceptive pills
 - Combined hormonal patch
 - Combined vaginal ring
 - Progestin-only contraceptive methods
 - Emergency contraceptive pills
 - Intrauterine contraception
 - Use of Copper IUDs for emergency contraception
 - Barrier contraceptive methods
 - Fertility awareness methods
 - Lactational amenorrhea method
 - Coitus interruptus
 - Female and male sterilization

+ WHO/CDC MEC for Contraceptive Use

Category	Description
1	No restriction for the use of the method
2	Advantages of using the method generally outweigh the theoretical or proven risks
3	Theoretical or proven risks usually outweigh the advantages of using the method
4	A condition that represents an unacceptable health risk if the contraceptive method is used

+ Category Interpretations

- When clinical judgment is available
 - Category 1 – use the method in any circumstances
 - Category 2 – Generally use the method
 - Category 3 – The method is not usually recommended unless other more appropriate methods are not available or not acceptable
 - Category 4 – Method not to be used
- When clinical judgment is limited
 - Category 1 or 2 – Use the method
 - Category 3 or 4 – Do not use the method

+ Differences between CDC and WHO for COC²

- Breastfeeding
 - CDC – Category 3 for <1 mo postpartum and Category 2 for 1mo to <6 months
 - WHO – Category 4 for <6 weeks postpartum and Category 3 for >= 6 weeks to <6 months postpartum
- DVT/PE
 - History of DVT/PE, not on anticoagulant with lower risk for recurrent DVT/PE (no risk factors) – Category 3 by the CDC and 4 by WHO
 - DVT/PE and established on anticoagulant therapy for at least 3 months with lower risk for recurrent DVT/PE (no risk factors) – Category 3 by CDC and 4 by WHO

+ Differences between CDC and WHO for POP, DMPA, & Implants²

- Breastfeeding
 - Category 2 for <1 mo postpartum by the CDC and Category 3 by the WHO for < 6 weeks postpartum
- DVT/PE
 - Acute DVT/PE – Category 2 by the CDC and Category 3 by the WHO

POP – progestin only pills
 DMPA – Depo- medroxyprogesterone acetate

+ Differences between the CDC and WHO for Levonorgestrel-IUD²

- Postpartum (in breastfeeding or non-breastfeeding women), including post caesarean section
 - Insertion is a Category 2 by the CDC if <10 min after delivery of the placenta
 - WHO – Category 1 if not breastfeeding and 3 if breastfeeding for insertion <48 hours
 - 10 min after delivery of the placenta to <4 weeks is a Category 2 by the CDC
 - Category 3 by the WHO if >=48 hours to <4 weeks
- DVT/PE
 - Acute DVT/PE – Category 2 by the CDC (Category 3 by the WHO)
- Valvular heart disease – complicated (pulmonary hypertension, risk for atrial fibrillation, history of subacute bacterial endocarditis)
 - CDC – Category 1 (WHO Category 2)
- Ovarian Cancer
 - CDC – Category 1 (WHO – Initiation=3, continuation =2)
- Uterine fibroids
 - CDC – Category 2 (WHO – Category 1 if no uterine distortion and 4 if uterine distortion is present)

+ Combined hormonal contraceptives in specific populations

+ Combined Hormonal Contraception in Obese women

- Increase in obese population
- Transdermal patch
 - Increased pregnancy rate in women weighing more than 90 kg when the patch was used
 - ACOG – patch should not be used as first-line option in obese individuals

+ Combined Oral Contraceptives in Obese Women

- Data
 - Limited data, inconsistent results
 - Studies have shown increased risk of unintended pregnancy in obese women
- Pharmacokinetics
 - Peak hormone levels are lower in obese women but trough levels similar³
- Explanations
 - Possible increased basal metabolic rates and increased hepatic enzyme activity in obese women
 - Increase hormone sequestration into adipose tissue in obese women

+ Hormonal contraception in obese women: recommendations

- ACOG recommendations for obese women
 - Advise obese women about the risk for decreased efficacy of COC
 - Suggest longer-acting progestin only methods or non-hormonal options

+ Hormonal contraceptives in women over age 35

- Advantages
 - Contraception protection
 - Increase in BMD – possibly
 - Decrease in vasomotor symptoms
- Risks
 - Cardiovascular disease
 - Venous thromboembolism (VTE)
 - Ischemic stroke
 - Breast cancer

+ Hormonal contraception in women >35 years

- Recommendations
 - ACOG and WHO
 - Use of COC (less than 50 mcg of estrogen) can be considered in healthy, nonsmoking women
 - Do not use in women >35 with migraines (with or without aura), HTN, or dyslipidemia, current smokers, type 1 or 2 diabetes

+ Risk of thrombosis with hormonal contraceptives

+ VTE with hormonal contraception

- Concern with the patch and VTE has been established
- Overall risk of VTE with low dose oral contraceptives containing less than 50 mcg of estrogen is 4 times higher in a user than non-user
- Relative risk of VTE associated with pregnancy is about a 6-8 fold increase when compared to non-hormonal contraceptive users
- Absolute incidence of VTE associated with COC is estimated to be 9-18 cases per 100,000 women per year

+ Drospirenone and risk of thrombosis

- Drospirenone, a 4th generation progestin
 - Parent compound is spironolactone
 - Antimineralocorticoid and anti-estrogen effects
- Mechanism of thrombosis by COC⁴
 - 3rd generation progestins – greater effect on procoagulant, anticoagulant, and fibrinolytic pathways
 - Increased resistance to the anticoagulant effect of activated protein C by some progestins
 - Higher levels of sex hormone binding globulin from the positive effect of the estrogen

+ Drospirenone and Thrombosis

- Early studies showed risk of VTE with drospirenone was similar to other progestins
- 2 recent studies have shown increased risk of VTE with drospirenone
- van Hylckama, et al.⁵
 - 1,524 patients with first episodes of DVT or PE were compared to 1,760 controls
 - All subjects were premenopausal <50 years and not pregnant
 - Results
 - Oral contraceptives increased risk of VTE 5 fold over non-users and risk appeared to be associated with estrogen dose and progestin
 - Compared with non-users, risk of VTE
 - Increased 3.6 fold with levonorgestrel
 - Increased 5.9 fold with norgestimate
 - Increased 6.3 fold for drospirenone
 - Increased 7.3 fold for desogestrel
 - Weakness of study – very few patients were taking drospirenone (12 with DVT and 7 with PE)

+ Drospirenone and VTE

- 2nd study by Lidegaard and colleagues⁶
- 10.4 million women years recorded, 3.3 million women years of oral contraceptive therapy and 4,213 venous thrombotic events
- Drospirenone use made up 131,541 woman years
- Absolute risk of VTE per 10,000 women years in non-users was 3.01 compared with 6.29 in oral contraceptive users
- Compared with levonorgestrel, risk of VTE was
 - 1.19 with norgestimate
 - 1.82 with desogestrel
 - 1.64 with drospirenone

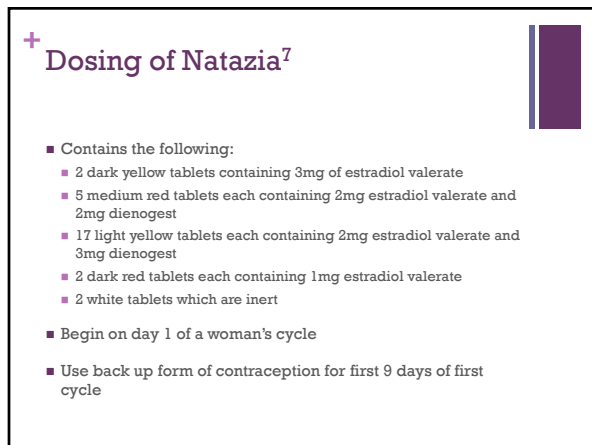


+ New COC – 4 phasic formulation

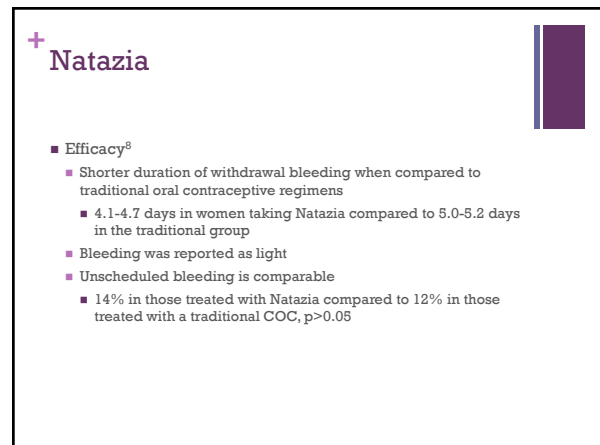
Pop Quiz:

What are the other formulations currently available for combined oral contraceptives?

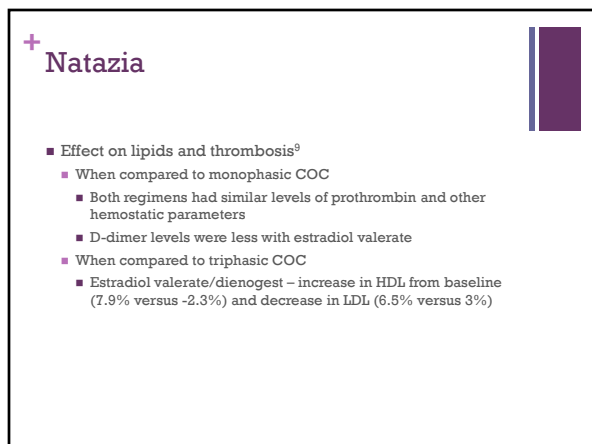
- Natazia (estradiol valerate and Dienogest)
 - Estradiol valerate –
 - synthetic form of the naturally occurring estradiol
 - prodrug
 - metabolized to estradiol
 - Dienogest
 - Has specific endometrial and antiandrogenic activity
 - Strong progestational activity
- Stepped dosing
 - Decreasing amounts of estrogen, increasing amounts of progestin



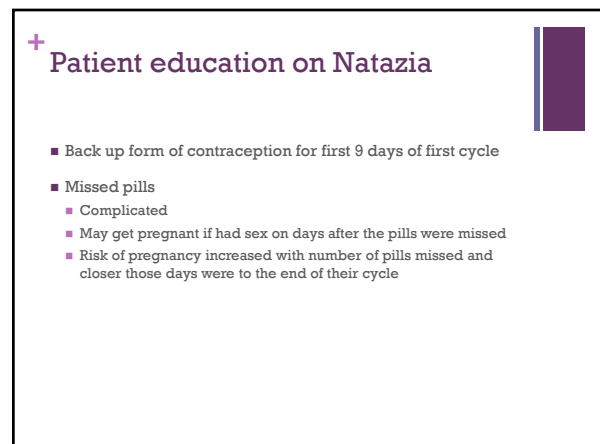
- Contains the following:
 - 2 dark yellow tablets containing 3mg of estradiol valerate
 - 5 medium red tablets each containing 2mg estradiol valerate and 2mg dienogest
 - 17 light yellow tablets each containing 2mg estradiol valerate and 3mg dienogest
 - 2 dark red tablets each containing 1mg estradiol valerate
 - 2 white tablets which are inert
- Begin on day 1 of a woman's cycle
- Use back up form of contraception for first 9 days of first cycle



- Efficacy⁸
 - Shorter duration of withdrawal bleeding when compared to traditional oral contraceptive regimens
 - 4.1-4.7 days in women taking Natazia compared to 5.0-5.2 days in the traditional group
 - Bleeding was reported as light
 - Unscheduled bleeding is comparable
 - 14% in those treated with Natazia compared to 12% in those treated with a traditional COC, p>0.05



- Effect on lipids and thrombosis⁹
 - When compared to monophasic COC
 - Both regimens had similar levels of prothrombin and other hemostatic parameters
 - D-dimer levels were less with estradiol valerate
 - When compared to triphasic COC
 - Estradiol valerate/dienogest – increase in HDL from baseline (7.9% versus -2.3%) and decrease in LDL (6.5% versus 3%)

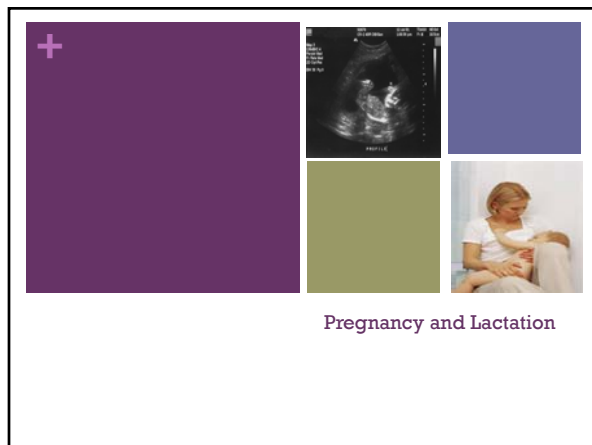


- Back up form of contraception for first 9 days of first cycle
- Missed pills
 - Complicated
 - May get pregnant if had sex on days after the pills were missed
 - Risk of pregnancy increased with number of pills missed and closer those days were to the end of their cycle



+ Emergency Contraception Review

- August 2006 – Plan B available to women 18 years of age and older with a prescription
- August 2009 – Plan B One Step is approved
 - Plan B One Step and Plan B – available without a prescription to women 17 years of age and older
 - Plan B One Step and Plan B – available by prescription for women younger than 17
- Plan B (levonorgestrel 0.75mg) – take 1 tablet as soon as possible after unprotected intercourse and a second tablet 12 hours later
- Plan B One Step (levonorgestrel 1.5mg) – Take 1 tablet as soon as possible after unprotected intercourse



+ Background

- Establishing risk or safety of drugs in pregnancy
 - Animal studies
 - Compare outcomes of pregnancy in animals given drug versus controls
 - Doses given generally much higher than those expected to be used in humans
 - Common models include monkeys, rabbits,
 - Generally good indicator
 - Exception: thalidomide, misoprostol

+ Background

- Establishing risk or safety of drugs in pregnancy
 - Human studies
 - Case reports
 - Epidemiologic studies
 - Post-marketing surveillance
 - International reporting
 - Meta-analyses
 - Long-term studies

+ FDA Categories

- Overview
 - 5 categories (Category A, B, C, D, and X)
 - Based on clinical data (animal, human) and estimated risk: benefit ratio if drug is given
 - In 2007 FDA began the process to remove the risk categories from drug labels
- Problems
 - Categories A and B cannot be equated to complete safety
 - The categories do not show a graduation of risk, where X is the highest risk and A is the lowest
 - Some products are labeled category X because there is no benefit to the mother (eg COC)
 - All drugs within the same category do not share the same risk
 - Categories do not consider exposure timing, dose, route, duration, or frequency
 - Categories do not address incidence, severity, or reversibility

+ Pregnancy Categories

- Category may change based on trimester of pregnancy or duration of exposure
 - Ibuprofen is Category C for 1st and 2nd trimesters but is Category D in the 3rd trimester.
- Category may be different for specific agents within a class of drugs
 - Diuretics: HCTZ is Category B; spironolactone is Category C.
- Category may change with accumulating clinical experience
 - Sertraline (Zoloft) was initially Category B then changed to Category C.

+ FDA Pregnancy and Lactation Labeling

- May 2008 FDA published a proposed regulation¹⁰
 - Information for both pregnancy and lactating women will be presented in 2 consecutive label subsections: "Pregnancy" and "Lactation"
 - All drugs approved on or after June 20, 2001 will ultimately be required to follow these requirements when a final rule publishes
 - Pregnancy categories will be eliminated from labeling and prescribing information

+ Proposed FDA labeling changes for Pregnancy and Lactation

- Pregnancy section
 - 3 major subsections:
 - Fetal Risk Summary
 - Clinical Considerations
 - Data
- Lactation Section
 - 3 major subsections
 - Risk Summary
 - Clinical Considerations
 - Data

+ OTC Recommendations of Common Ailments During Pregnancy

+ Nausea and Vomiting

- Vitamin B6– 10mg q8h (25mg q8h if needed)
- Doxylamine (10mg) -Pyridoxine (10mg)
 - Was available from 1958-1983 as Bendectin
 - Voluntarily removed
- Antihistamines
 - Meclizine is drug of choice - low teratogenicity – 25mg q4-6h prn
 - Diphenhydramine 25-50mg po q4-6h
 - Dimenhydrinate 50 to 100 mg PO q4-6h

+ Alternative therapies

- Ginger
 - Some concerns for safety
 - May increase risk of bleeding due to inhibition of platelet aggregation
 - AE – belching, bloating, gas, bad taste
 - Listed as an alternative according to ACOG
- Acupressure
 - Neiguan point (3 fingers width above the wrist on the inner arm surface)
 - Wrist bands sold OTC – Reliefband
 - Safe, inexpensive, and readily available

+ GERD/Heartburn

- Calcium based antacids are 1st line
- Aluminum and magnesium containing antacids are also low risk
- H2RA's
 - Cimetidine and ranitidine are drugs of choice
- PPI's
 - Omeprazole
 - Has documented embryonic and fetal toxicity, but risk is low
 - Considered drug of choice for class
- Sucralfate – limited data, but in theory is not absorbed orally and may be effective
- Avoid sodium bicarbonate and magnesium trisilicates

+ Constipation/Diarrhea

- Constipation
 - Polyethylene glycol – low risk and preferred treatment
 - Docusate – low risk
 - Senna and Bisacodyl – low risk for short term use
 - Avoid castor oil and mineral oil
- Diarrhea
 - Loperamide – has fetotoxicity and should be avoided
 - Avoid bismuth containing compounds

+ Common Cold/Cough

- Treatment
 - Avoid combination products/ products with alcohol
 - Antihistamine
 - Chlorpheniramine, diphenhydramine – first line
 - Loratadine, cetirizine – alternative according to ACOG, but not during 1st trimester
 - Decongestants
 - Pseudoephedrine
 - **Avoid in 1st trimester**
 - Phenylephrine – has been associated with major and minor fetal defects
 - Oxymetazoline – nasal decongestant of choice
 - Antitussives/expectorants
 - Guaifenesin – increased risk of inguinal hernia, avoid in 1st trimester
 - Dextromethorphan – not a major teratogen
 - Don't recommend, no benefit

+ Headache/Fever/Pain

- Acetaminophen is drug of choice
- Avoid NSAIDS
 - Used late in pregnancy can cause persistent pulmonary hypertension and premature closing of ductus arteriosus
 - Used around conception can block blastocyte implantation
 - Have been known to cause miscarriages

+ OTC Recommendations for Common Ailments while Breastfeeding

+ Analgesics during Breastfeeding

- Ibuprofen and Acetaminophen are drugs of choice
- Avoid aspirin due to risk of Reye's syndrome

+ Cough/Cold/Allergic Rhinitis

- Decongestants
 - Avoid pseudoephedrine and phenylephrine – can decrease milk supply and cause irritability in infant
- Antihistamines
 - Loratadine preferred
 - 1st generation may cause drowsiness and irritability in infants
- Cough products
 - Guaifenesin – unlikely to cause harm
 - Dextromethorphan – unlikely to cause harm

+ GI

- GERD/Heartburn/Stomach upset
 - Antacids – calcium, aluminum, and magnesium containing – are safe
- H2RA's
 - Famotidine preferred, but all are safe
- PPI's
 - omeprazole is safe
 - No data on lansoprazole – avoid use
- Avoid bismuth products
- Diarrhea/Constipation/Intestinal Gas
 - Loperamide
 - Psyllim, docusate, senna, bisacodyl
 - Simethicone
 - Miralax

+ Resources for Pregnancy

- Some resources for determining risk of drug therapy during pregnancy
 - FDA Pregnancy Categories (package inserts)
 - Teratogen Information System (TERIS)
 - Textbooks
 - General therapeutic texts
 - *Drugs in Pregnancy and Lactation* by Briggs GG
 - *Medication Safety in Pregnancy and Breastfeeding* by Koren G.
 - *Drugs During Pregnancy and Lactation* by Schaefer C.
 - *Chemically Induced Birth Defects* by Schardein JL.
 - *Catalog of Teratogenic Agents* by Shepard TH.
 - Organization of Teratology Information Specialists (OTIS)
 - otispregnancy.org

+ Resources for Lactation

- American Academy of Pediatrics, Transfer of Drugs and Chemicals Into Human Milk
- *Drugs in Pregnancy and Lactation* by Gerald Briggs
- *Medications and Mother's Milk* by Thomas Hale
- LactMed - <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>
- www.mothersrisk.org
- <http://neonatal.ttuhscc.edu/lact/>

+ Menopause



+ Review of Women's Health Initiative

- Stopped in 2002 because health risks exceeded health benefits over an average of 5.2 years of follow up
- Participants received CEE 0.625 mg/d plus MPA 2.5mg/d (Prempro[®]) or placebo
- Results
 - 29% increase risk of heart disease events – 7 more in 10,000 females/year
 - 41% increase risk of stroke – 8 more per 10,000 females/year
 - 111% increase risk of blood clots in lungs – 10 more per 10,000 females/year
 - 26% increase risk of breast cancer – 8 more per 10,000 females/year
- Benefits
 - 37% decrease risk of colorectal cancer – 6 fewer cases per 10,000 females/year
 - 34% decrease risk of fracture – 5 fewer cases per 10,000 females/year

+ Estrogen Only Arm of WHI

- 10,739 postmenopausal women, 50-79 years with prior hysterectomy randomly assigned to receive either 0.625 mg/d of CEE or placebo
- Trial ended early in 2/04 due to lack of benefit
- Results
 - 39% increase risk of stroke -12 additional strokes per 10,000 females/year
 - 39% decrease risk of hip fractures – 6 fewer per 10,000 females/year
 - Estimated excess risk for all monitored events was a non-significant 2 events per 10,000 person years.
 - No increase risk of heart disease or breast cancer

+ Hormone Replacement Therapy

- North American Menopause Society (NAMS) published position statement on estrogen and progestogen use in postmenopausal women in 2010¹¹

+ Treatment of menopausal symptoms

- Vasomotor symptoms
 - Estrogen therapy with or without a progestin
- Vaginal symptoms
 - Estrogen therapy (estrogen, estrogen/progestin therapy, or local vaginal estrogen therapy)
 - If solely for urogenital atrophy – local vaginal estrogen therapy is recommended
- Sexual function
 - Systemic or local hormone therapy can help with dyspareunia

+ Cardiovascular effects

- Coronary Heart Disease
 - Estrogen therapy (ET) arm of WHI showed that ET may reduce CHD risk when initiated in younger and more recently postmenopausal women when analyzed by age and time at initiation
 - Secondary analysis of WHI – statistically significant reduction in MI, coronary revascularization, and coronary death in women randomized to ET during ages 50-59
 - Data from ET and estrogen/progestin therapy (EPT) arms of WHI indicate that women who initiate HT more than 10 years beyond menopause are at increased risk for CHD

+ Cardiovascular Effects

- Stroke
 - Recent analysis of combined results from WHI EPT and ET showed that hormone therapy (HT) in younger women (50-59) at study entry had no significant effect on risk of stroke
 - No studies show that HT is effective for reducing risk of recurrent stroke or prevention of first stroke
 - May increase rate of first strokes in women initiating HT over age 60
 - Cannot recommend for the primary or secondary prevention of stroke
- VTE
 - Increased risk of VTE with oral HT, magnitude of risk decreases some over time
 - Lower doses of ET may have less VTE risk but no randomized controlled trial (RCT) to confirm

+ Diabetes mellitus

- Inadequate evidence to recommend HT as sole or primary indication for prevention of DM in peri- or postmenopausal women
- In women with T2DM – transdermal ET may offer advantages
 - Triglyceride levels are not further increased
 - Thrombotic factors are not further increased
 - Adverse alterations in BP have only been reported with oral therapy

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Pop Quiz:

Progestin therapy is added to HT in women with an intact uterus for what reason?

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Cancer risk and HT

- Endometrial Cancer
 - Unopposed systemic ET in postmenopausal women with an intact uterus is associated with increased endometrial cancer
 - If history of endometrial cancer, should not receive HT at all
- Breast Cancer
 - EPT use beyond 3-5 years is associated with an increase in the diagnosis of breast cancer
 - Women in the ET group of WHI trial had no increased risk of breast cancer, and had a decreased risk of invasive breast cancer
 - When ET extended beyond 10-15 years in observational studies breast cancer risk increased
 - HT has not been proven to be safe for women with a history of breast cancer
- Ovarian Cancer
 - Association between ovarian cancer and HT beyond 5 years is rare to very rare
- Lung Cancer
 - Initiating EPT therapy in older women with a history of smoking may promote the growth of existing lung cancers
 - Possibly some protection against lung cancer though in women <60 years old
- Colorectal Cancer
 - New analysis from WHI shows that HT does not reduce the risk of colorectal cancer

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Cognitive aging and dementia

- WHI Memory study
 - Reported an increase in dementia with HT use in women 65-79
- No clinical trials address the use of HT during the menopause transition and early postmenopause time with regards to long-term cognitive consequences
- Conclusion
 - HT cannot be recommended at any age for preventing cognitive aging or dementia

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Summary of hormone therapy

- Use lowest effective dose of estrogen
- Administer a progestin to women with an intact uterus who are also on ET to prevent endometrial cancer
- Transdermal therapy has no significant increase in triglycerides, no change in C-reactive protein, little effect on blood pressure, no increase in SHBG
- Do not use in women older than 60 years who have experienced natural menopause without a compelling indication
- More research is needed to address individual benefits and adverse effects from each type of estrogen, progestin, route of administration, and timing of therapy

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Questions

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