A4M | MEDICINE REDEFINED

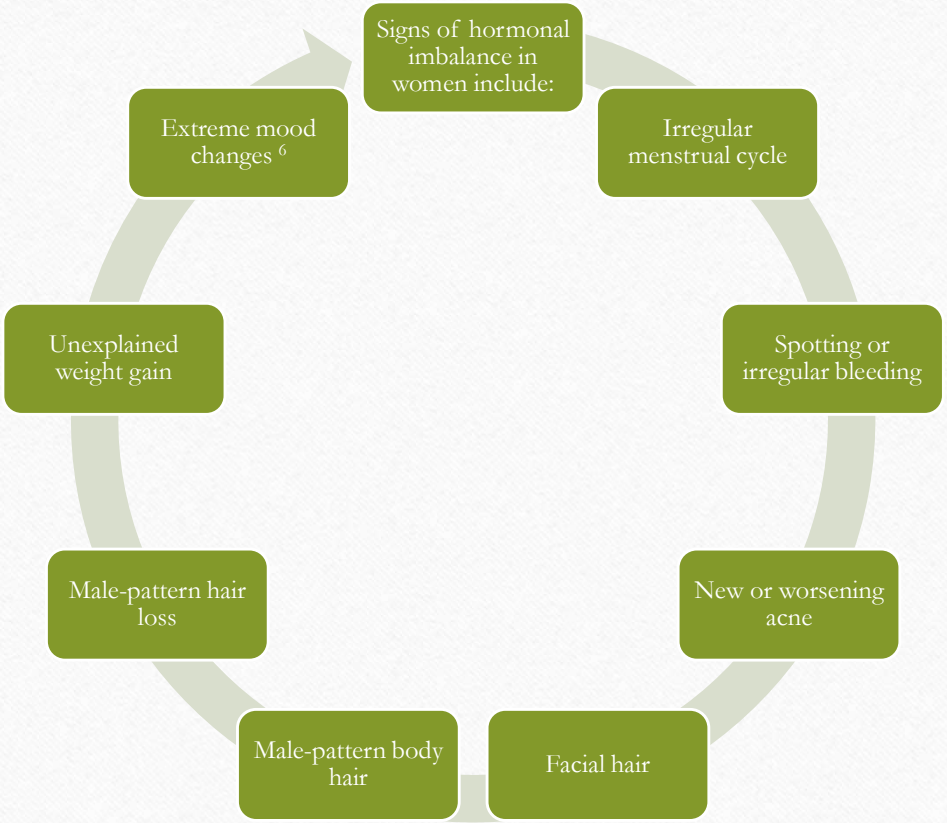
ENDOCRINE BALANCE AND BIO-IDENTICAL HORMONE RESTORATION

Symposium

The Science Behind HRT

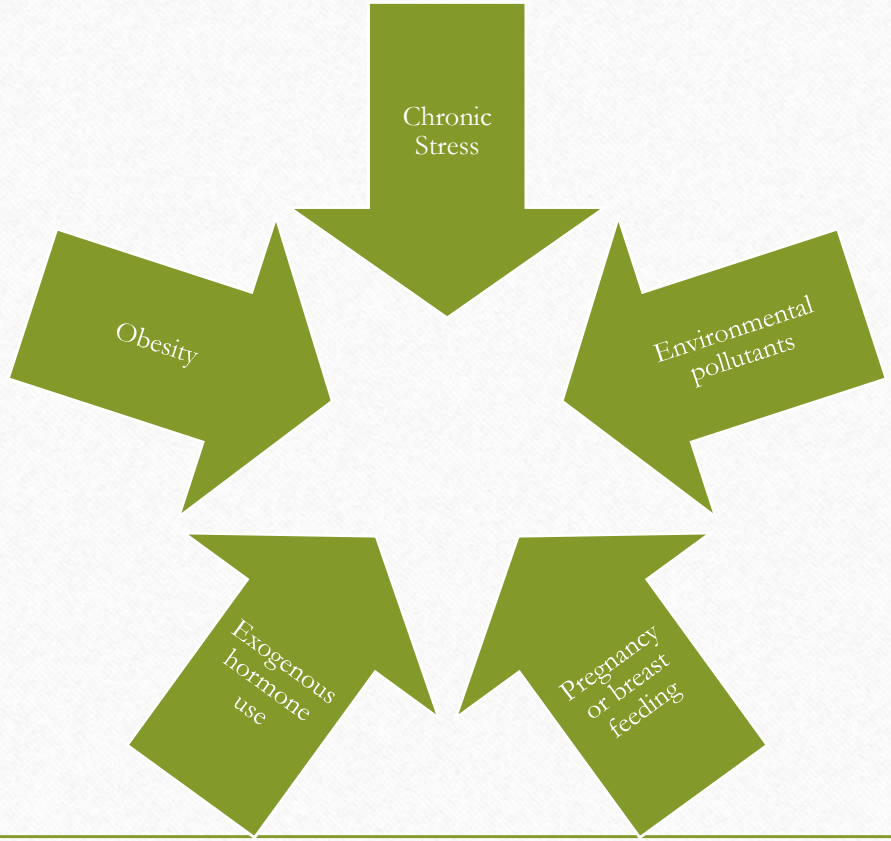
Sahar Swidan, Pharm.D., ABAAHP, FAARFM, FACA

Signs of Hormonal Imbalance



Treasure NO, Johnkennedy N, Chinyere O, Amarachi IP, Chioma N. The Perspective of Hormonal Imbalance in Humans: A Review. Acta Scientific Clinical Case Reports Volume. 2022 Nov;3(11).

Causes of Hormonal Imbalance



Decline in HRT use

- The 'Women's Health Initiative' conducted a randomized controlled trial to assess the use of continuous combined menopausal hormone therapy
- Study was stopped due to increased risk of breast cancer, coronary heart disease, stroke and pulmonary embolism
- Consequently, there has been a steep decline in monopausal hormone therapy around the world

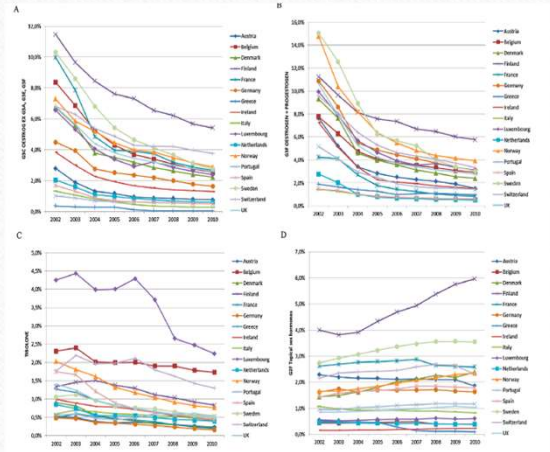


Fig. 3. Changes in estimated proportion of women aged 45–69 years old, using different MHT regimens, in 17 European countries: (A) estrogens only or combined to a separate progestin, (B) estrogens combined to progestins, (C) tibolone and (D) topical vaginal estrogen.

Ameye et al Maturitas. 2014;79(3

Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality
The Women's Health Initiative Randomized Trials

- Among postmenopausal women who participated in 2 parallel randomized trials of estrogen plus progestin and estrogen alone, all-cause mortality rates for the overall cohort in the pooled trials were not significantly different for the hormone therapy groups vs the placebo groups (27.1% vs 27.6%; hazard ratio, 0.99 [95% CI, 0.94-1.03]).

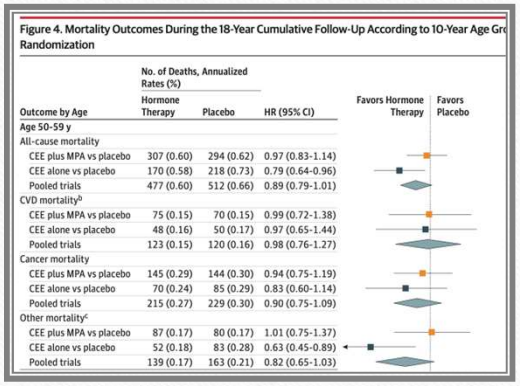
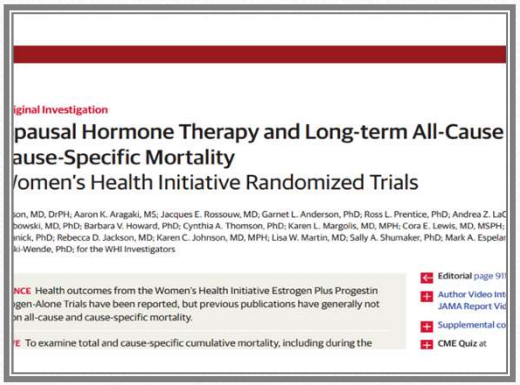


Figure 4. Mortality Outcomes During the 18-Year Cumulative Follow-Up According to 10-Year Age Gr
Randomization

Outcome by Age	No. of Deaths, Annualized Rates (%) Hormone Therapy	Placebo	HR (95% CI)
Age 50-59 y			
All-cause mortality			
CEE plus MPA vs placebo	307 (0.60)	294 (0.62)	0.97 (0.83-1.14)
CEE alone vs placebo	170 (0.58)	218 (0.73)	0.79 (0.64-0.96)
Pooled trials	477 (0.60)	512 (0.66)	0.89 (0.79-1.01)
CVD mortality[b]			
CEE plus MPA vs placebo	75 (0.15)	70 (0.15)	0.99 (0.72-1.38)
CEE alone vs placebo	48 (0.16)	50 (0.17)	0.97 (0.65-1.44)
Pooled trials	123 (0.15)	120 (0.16)	0.98 (0.76-1.27)
Cancer mortality			
CEE plus MPA vs placebo	145 (0.29)	144 (0.30)	0.94 (0.75-1.19)
CEE alone vs placebo	70 (0.24)	85 (0.29)	0.83 (0.60-1.14)
Pooled trials	215 (0.27)	229 (0.30)	0.90 (0.75-1.09)
Other mortality[c]			
CEE plus MPA vs placebo	87 (0.17)	80 (0.17)	1.01 (0.75-1.37)
CEE alone vs placebo	52 (0.18)	83 (0.28)	0.63 (0.45-0.89)
Pooled trials	139 (0.17)	163 (0.21)	0.82 (0.65-1.03)

Favors Hormone Therapy | Favors Placebo



iginal Investigation

pausal Hormone Therapy and Long-term All-Cause
ause-Specific Mortality
/omen's Health Initiative Randomized Trials

ion, MD, DrPH; Aaron K. Aragaki, MS; Jacques E. Rossouw, MD; Garnet L. Anderson, PhD; Ross L. Prentice, PhD; Andrea Z. LaC
bowski, MD, PhD; Barbara V. Howard, PhD; Cynthia A. Thomson, PhD; Karen L. Margolis, MD, MPH; Cora E. Lewis, MD, MSPH;
nick, PhD; Rebecca D. Jackson, MD; Karen C. Johnson, MD, MPH; Lisa W. Martin, MD; Sally A. Shumaker, PhD; Mark A. Espelar
ki-Wende, PhD; for the WHI Investigators

NCE Health outcomes from the Women's Health Initiative Estrogen Plus Progestin
gen-Alone Trials have been reported, but previous publications have generally not
n all-cause and cause-specific mortality.

E To examine total and cause-specific cumulative mortality, including during the

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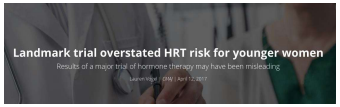
Current Role of HT

- Safe, effective option to initiate in healthy women <60 years of age or less than 10 years after menopause



Effects of Hormone Therapy on survival, cancer, cardiovascular and dementia risks in 7 million menopausal women over age 65: a retrospective observational study

Seo H. Baik, Fitsum Baye, Clement J. McDonald

doi: https://doi.org/10.1101/2022.05.25.22275595

However, the situation is complicated

- However, the situation is complicated
  - For women post hysterectomy- estrogen is all good
  - For women with a uterus, estrogen alone, without progestin cycling, is a risk for endometrial cancer among women with intact uteruses
  - Use of progesterone prevents endometrial hyperplasia which can progress to cancer.):
    - Common regimen is 200 milligrams (mg) per day of micronized progesterone,, taken, for 12 continuous days per 28-day menstrual cycle.
  - An alternative is daily progestin which suppresses menstrual periods. But given the risks we observed with EPT, use of progestin only in latter part of cycle is probably a better choice

Main findings 2

- in our Cox Regression analysis, ET use, overall was associated with a significant, 19% reduction in all cause mortality risk compared to no ET use !
- And was associated with a reduced risk of breast, lung and colorectal cancers – all also reported by others
- Its use was also associated a reduced risk of CHF, VTE, Stroke, AMI and dementia relative to no ET use
- **The Good Witch of the South (the Wizard of Oz)

Main findings 2

- Risk reduction was significantly greater for E2 vs. CEE, vaginal and transdermal vs. oral, and low or medium. doses (vs. high dose)
- EPT use was associated with a significantly increased risk of breast cancers across all types, routes, and strengths.
  - The Bad Witch of the West

Association with all-cause mortality

- In our study using Cox Regression, the use of Estrogen monotherapy (ET)was associated with 19% reduction in mortality risk, considering all ET preparations together.
- These results are consistent with other studies that reported mortality among HT users.[1,2]

1. Symer MM, Wong NZ, Abelson JS, Milsom JW, Yeo HL. Hormone Replacement Therapy and Colorectal Cancer Incidence and Mortality in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Clin Colorectal Cancer. 2018 Jun 1;17(2):e281–8.
2. Henderson BE, Paganini-Hill A, Ross RK. Decreased Mortality in Users of Estrogen Replacement Therapy. *Arch Intern Med.* 1991;151(1):75–78. doi:10.1001/archinte.1991.00400010095012
3. Bush TL, Cowan LD, Barrett-Connor E, et al. Estrogen Use and All-Cause Mortality: Preliminary Results From the Lipid Research Clinics Program Follow-up Study. *JAMA.* 1983;249(7):903–906.

Association with CV disease

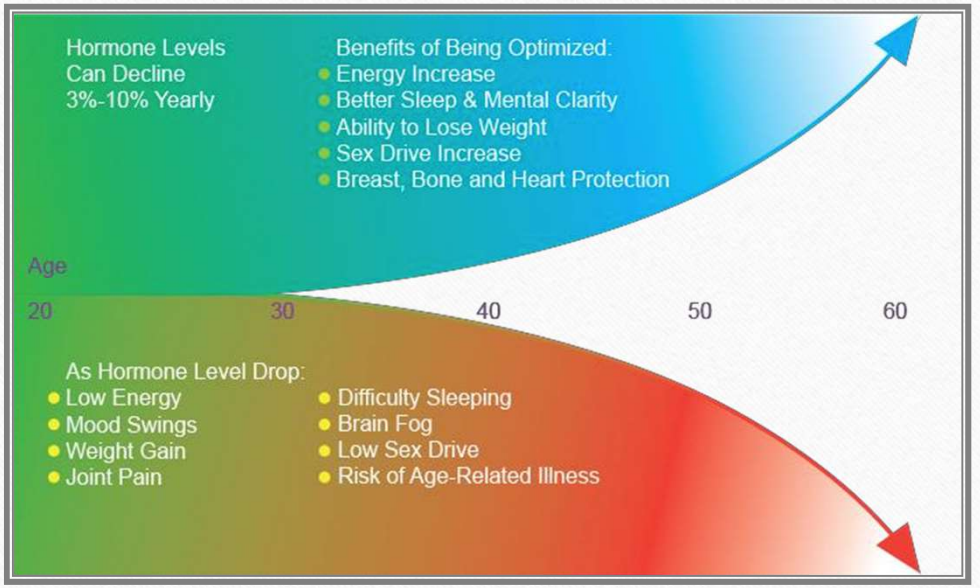
- The WHI, CEE (estrogen) had no association with coronary heart disease
- We saw a small increased ischemic heart disease (IHD) risk with ET use. However, this increased risk was concentrated in the use of high (9% risk) and medium (2% risk) doses of ET.
- Low dose of ET monotherapy exhibited a salubrious, 1%, decrease in risk for IHD.

Estrogen use in menopause

- In women without uterus , estrogen monotherapy is good !!
- It reduces mortality risk and risk of many cancers - a no brainer
- Monotherapy only safe after a hysterectomy
  - Women who retain their uterus must take some progestin along with their estrogen –e.g. 200 mg micronized progesterone on 12-14 days per cycle
- We don't know exactly how cyclic progesterone changes the risks associated with continuous progesterone with or without estrogen

Why BHRT is important

- Androgens peak for women in their twenties while they peak for men in their mid thirties
- Low testosterone in women and men results in an increased risk for:
  - Alzheimer's Disease
  - Cardiovascular Disease
  - Diabetes Mellitus



Targeted Receptors

Hormone Receptor Ligand Affinities (%)

	ERa	ERb	PRa	PRb	AR	GR	MR
Estradiol	100	100	0	0	0	0	0
Estrone	60	37	0	0	0	0	0
Estriol	14	21	0	0	0	0	0
Progesterone	0	0	50	50	0	10	100
Medroxyprogesterone acetate	0	0	115	115	5	29	160
Testosterone	0	0	1	1	100	0.2	1

Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. *Climacteric*. 2005;8 Suppl 1:3-63. doi:10.1080/13697130500148875

Tissue Effect

	Estrogen	Progesterone	Progestin	Testosterone
CNS	-Vasomotor sx improvement -cognitive improvement -mood improvement	-mood improvement -neuroprotective -memory improvement	Memory impairment	neuroprotective
CV	atherosclerosis preventative	cardioprotective	CHD events	-CHD events (varies by dose)
Bone	Increases BMD	Increases BMD	Decreases BMD	Increases BMD
Urinary tract	-improves LUTS -decreases UTI risk	Decreases bladder tone	-Increases bladder tone -Increases UTI risk	Improves LUTS
Hematologic	Coagulatory effects (higher risk oral vs transdermal)	Coagulatory effects unlikely	Coagulatory effects	-Polycythemia -coagulatory effects
Liver	-Lowers blood glucose -Hepatotoxic (oral)	Hepatotoxic (oral)	Hepatotoxic (oral)	Anti-inflammatory effects
Mammary gland	Regulates epithelial proliferation	Regulates epithelial proliferation	Impairs epithelial regulation	Regulates epithelial proliferation
Hair	Promotes growth	Promotes growth	Growth/loss *varies by agent	Potential loss

Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases [published correction appears in BMJ. 2019 Jan 15;364:l162]. *BMJ*. 2019;364:k4810. Published 2019 Jan 9. doi:10.1136/bmj.k4810
González-Orozco JC, Camacho-Arroyo I. Progesterone Actions During Central Nervous System Development. *Front Neurosci*. 2019;13:503. Published 2019 May 17. doi:10.3389/fnins.2019.00503
Miodrag A, Castleden CM, Vallance TR. Sex hormones and the female urinary tract. *Drugs*. 1988;36(4):491-504. doi:10.2165/00003495-198836040-00006

Benefit claims of BHRT

- Bioidentical hormones are plant derived (vs animal derived). This provides a benefit because receptors have only been exposed to bioidentical hormones, therefore receptors responded better to bioidentical compared to synthetic. They "match" hormones naturally occurring in body
  - Leads to lower risks and better efficacy when using BHRT
  - Identical structure, plant based, increased efficacy and decreased side effects associated with FDA approved products

Why are Women Choosing BHRT?

Drawn to “natural”

There is a perception that natural is better

There is an appeal to how HRT is marketed

“Individualized” or “customized” care

Allure of ”special ingredient” not commercially available

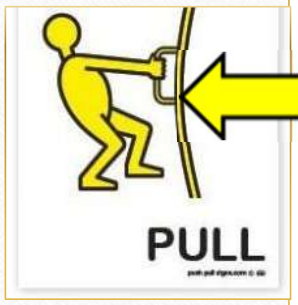
Ingredients such as Estriol

BHRT is improving overall health

Why are Women Choosing BHRT?

- The 'Push and Pull'

Motivations for using CBHT	# (%) of CBHT users
Push away from conventional therapies	
Fear and uncertainty about the safety of HT	17 (80.9%)
Distaste for conjugated estrogens, in particular	10 (47.6%)
Distrust of biomedicine and the pharmaceutical industry	20 (95.2%)
Push away from alternative therapies	
Ineffective symptom management	13 (61.9%)
Pull toward CBHT	
Effective symptom management	16 (76.2%)
Perception that CBHT is "safer" than conventional HT	16 (76.2%)
Desire for individualized treatment	12 (57.1%)
Enhanced clinical experience	13 (61.9%)



Thompson JJ, et al. *BMC Women's Health* 2017;17:97

Synthetic Hormones

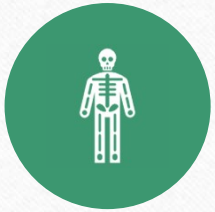
- Synthetic hormones have a different chemical structure, receptors do not provide the same response when binding occurs
  - May bind to the human hormone receptors in one tissue, but not in others
    - And vice versa, it might bind to other receptors that the endogenous hormone will not
  - The failure of synthetic hormones to bind with all the same receptors as endogenous hormones, as well as their binding to other non endogenous hormone receptors, creates adverse effects (e.g., tumors)

Concerns of BHRT

- Although bioidentical hormones are closely related in structure, they do NOT meet the definition of "natural"
  - They must still be chemically synthesized from a natural starting material to be the same molecular structure as humans
- Statements made about compounded BHRT may not have scientific support
- FDA is aware of reports of baldness in women who have used compounded BHRT products, had significantly higher than normal testosterone levels

NASEM Hearings

Review the current and historic use of compounded BHRT drug products to treat patients, including information about the medical condition(s) that these compounded drug products have been used to treat;

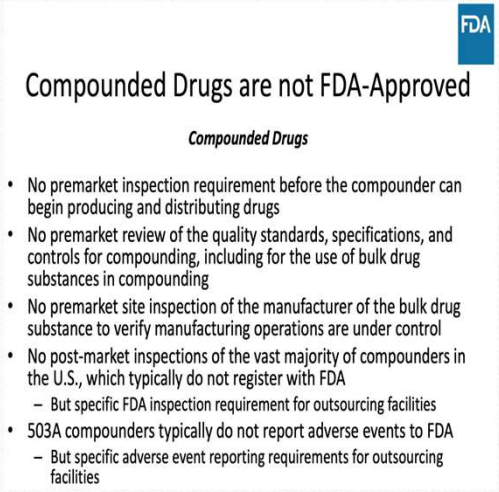


Describe the physical and chemical characteristics of compounded BHRT drug products (e.g., active ingredient, inactive ingredient(s), dosage forms, routes of administration, strengths);

Review and assess the available evidence (or lack of evidence) regarding the safety and effectiveness of compounded BHRT drug products;

Based on the available evidence, summarize findings and make recommendations with respect to- the clinical utility of compounded BHRT drug products;- whether the available evidence of safety and effectiveness supports use of compounded BHRT drug products to treat patients; and- the patient populations that might need a compounded BHRT drug product in lieu of an FDA-approved drug product.

Concerns from the FDA



Compounded Drugs are not FDA-Approved

Compounded Drugs

- No premarket inspection requirement before the compounder can begin producing and distributing drugs
- No premarket review of the quality standards, specifications, and controls for compounding, including for the use of bulk drug substances in compounding
- No premarket site inspection of the manufacturer of the bulk drug substance to verify manufacturing operations are under control
- No post-market inspections of the vast majority of compounders in the U.S., which typically do not register with FDA
  - But specific FDA inspection requirement for outsourcing facilities
- 503A compounders typically do not report adverse events to FDA
  - But specific adverse event reporting requirements for outsourcing facilities

Safety of Compounded BHT Products

What is the available scientific evidence on the safety of compounded BHT drug products and the strength of that evidence?

Do any of the reported safety risks associated with compounded BHT products depend on their characteristics (e.g., strength, dosage form)?

How does the available scientific evidence on the safety of compounded BHT drug products and strength of that evidence compare with that of FDA-approved drug products?

Are compounded BHT drug products associated with risks different from, or in addition to, those described in the labeling of comparable FDA-approved drug products?

- For example, class risks of estrogen products identified on FDA-approved labeling?

Area of Concern: Regulatory Oversight

- Compounded drugs are not reviewed by FDA for safety, efficacy, or manufacturing quality before marketing
- Most compounders do not report adverse events to FDA
- FDA has voiced concern over pharmacies misleading women and practitioners by unsupported claims of safety and greater efficacy than FDA-approved menopausal hormone therapies

Area of Concern: Future Research

"There is insufficient evidence regarding the safety and efficacy of compounded "bioidentical" hormone therapy for treatment of menopausal symptoms"

"Unable to identify any clinical trials comparing compounded hormone therapy for menopausal symptoms that met the criteria for inclusion"

"Due to growing interest and an increase in prescription of compounded hormones, the limitations in the evidence base emphasizes the priority that should be given to future research"

Grant MD, et al. *AHRQ Comparative Effectiveness Reviews*. 2015 Mar. pp 142-143.

Area of Concern: Clinical Safety and Utility of BHRT

- Lack of scientific evidence supporting claims of efficacy and safety
- Non-uniform dosing monitored by salivary hormone determinations
- Inconsistencies in manufacturing standards and state regulatory oversight
- Potential for product contamination and/or impurities
- **Lack of patient package inserts regarding anticipated risks**

Stuenkel CA and Manson JE. *JAMA Intern Med* 2017;177:1719-1720.

Area of Concern: Clinical Safety and Utility of BHRT

- Increased risk of Endometrial Cancer in women using BHRT compared with women using FDA approved therapies
  - Lack of randomized trials demonstrating safety of BHRT & endometrial cancer
  - Lack of adverse event reporting by compounding pharmacies

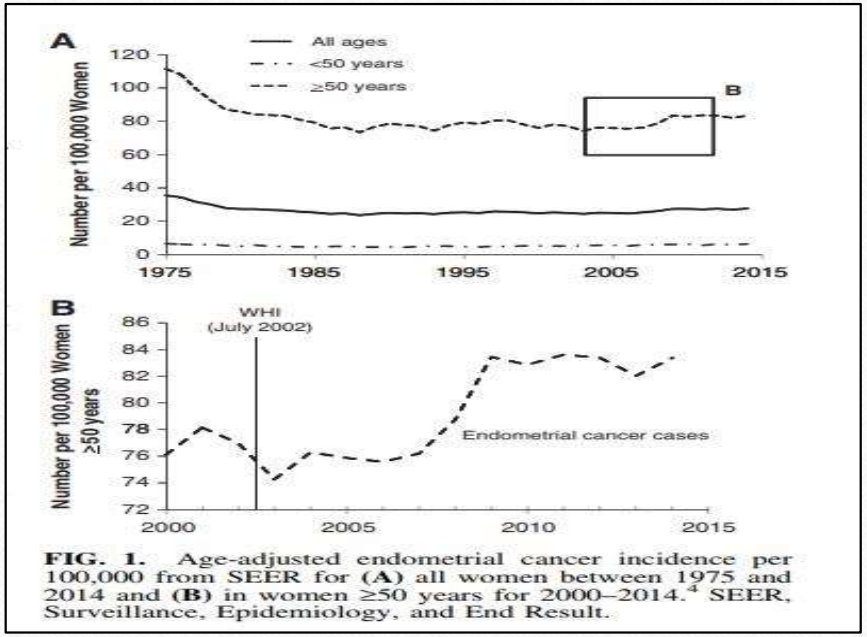


FIG. 1. Age-adjusted endometrial cancer incidence per 100,000 from SEER for **(A)** all women between 1975 and 2014 and **(B)** in women ≥50 years for 2000–2014.[4] SEER, Surveillance, Epidemiology, and End Result.

Stuenkel CA and Manson JE. *JAMA Intern Med* 2017;177:1719-1720; 1.Gass ML, *Menopause* 2015;22:1276-1284; 2.Pinkerton JV,Pickar JH. *Menopause* 2016;23:215-223.

The Panel Put Policy-Making Before Patient Need

An Independent Analysis of the FDA-Commissioned NASEM Report, The Clinical Utility of Compounded Bioidentical Hormone Therapy: A Review of Safety, Effectiveness, and Use

APRIL 2021

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Save Compounded Hormones

https://compounding.com/

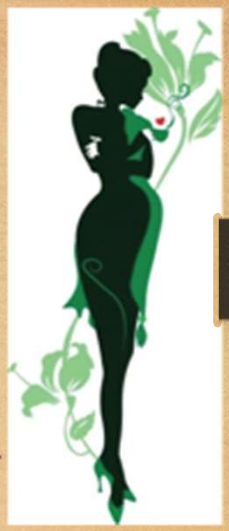
www.savehormones.org

Estrone

Maintains healthy thin uterine lining during menopause.

Estradiol

Maintains healthy uterine lining for possible pregnancy during reproductive years.



Estriol

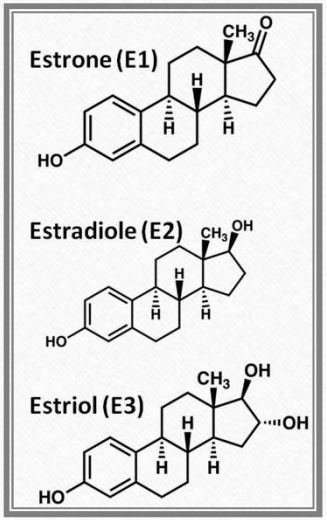
Maintains healthy thick uterine lining providing

Estrogen Uses

- Perimenopausal and menopausal symptom relief
  - Vasomotor symptoms
  - Prevent osteoporosis
- Hypogonadism (eg. genetic disorders)
- Derivatives/conjugates are used as contraceptives

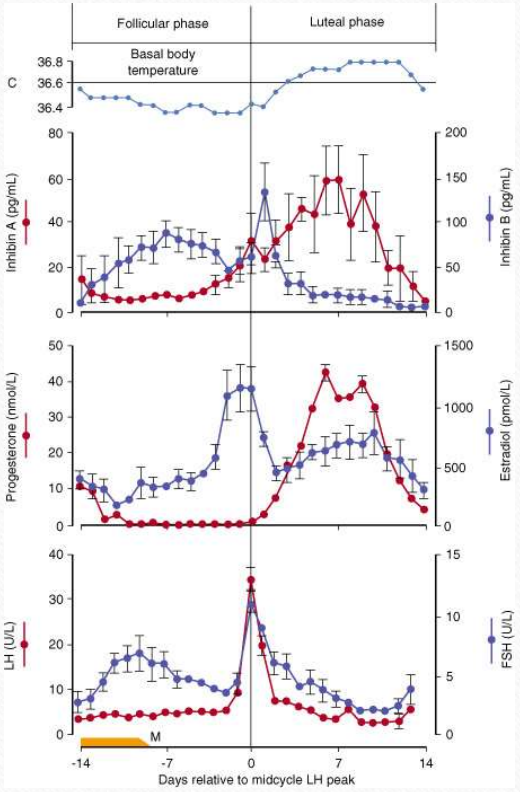
Biosynthesis of Estrogens

- 2% of circulating estradiol is free with the remainder bound to protein
  - 60% to albumin and 38% to the same gonadal steroid-binding globulin that binds testosterone
- In the liver, estradiol, estrone, and estriol are converted to glucuronide and sulfate conjugates
- All these compounds, along with other metabolites, are excreted in the urine
- Some secretion occur in bile and are reabsorbed into the bloodstream



Secretion of Estradiol

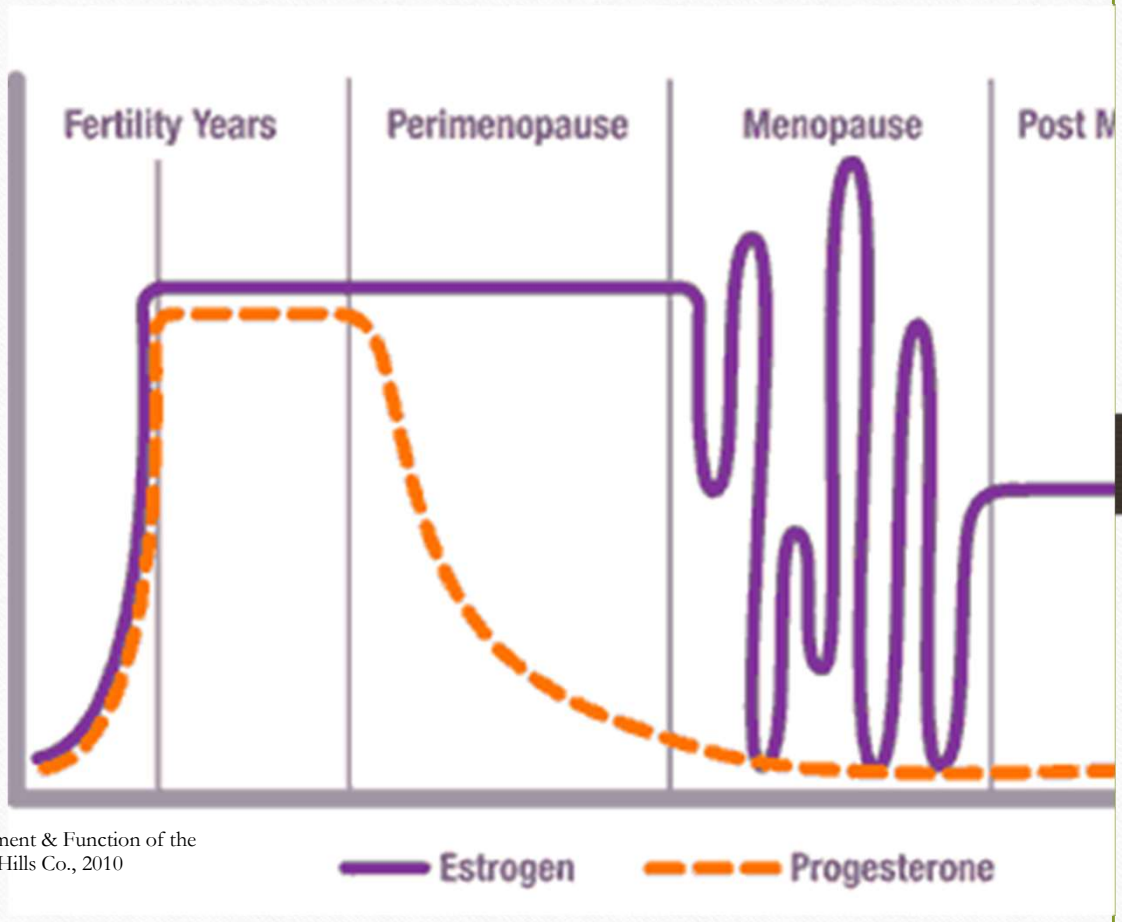
- The concentration of estradiol in the plasma during the menstrual cycle is shown
- Almost all of this estrogen comes from the ovary, and two peaks of secretion occur
  - One just before ovulation and one during the midluteal phase



Barrett KE, BBarman SM, Boitano S, Brooks HL. "Chapter 25. The Gonads: Development & Function of the Reproductive system" Ganong's Review of Medical Physiology. 23rd Ed. The McGraw-Hills Co., 2010

Secretion of Estradiol

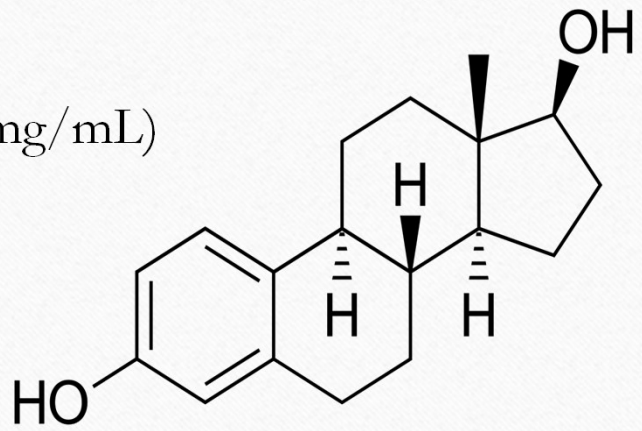
- Estradiol secretion rate is 36 mcg/d (133 nmol/d) in the early follicular phase, 380 mcg/d just before ovulation and 250 mcg/d during midluteal phase
- After menopause, estrogen secretion declines to low levels
- The estradiol production rate in men is about 50 mcg/d (184 nmol/d)



Barrett KE, BBarman SM, Boitano S, Brooks HL. "Chapter 25. The Gonads: Development & Function of the Reproductive system" Ganong's Review of Medical Physiology. 23rd Ed. The McGraw-Hills Co., 2010

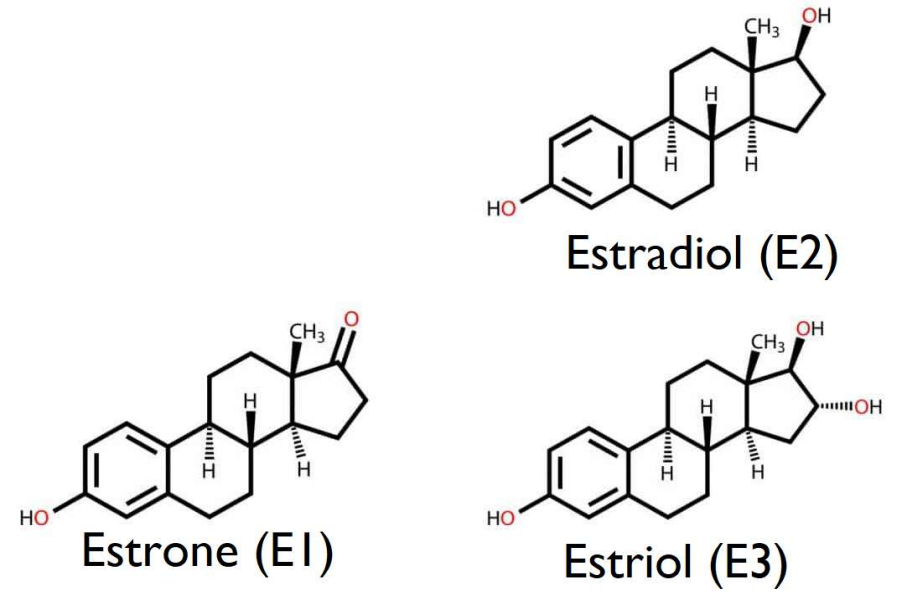
Estrogen Chemistry

- Estradiol is nonpolar with poor water solubility (0.9 mg/mL)
- It is lipophilic: logPoct/water = 3.94
- It readily crosses cell membranes
- Binds to estrogen receptors (ER) which
- modulate DNA transcription



Estrogen Potency

- Estradiol is:
- 10x as potent as estrone
- 100x as potent as estriol



Estradiol Pharmacokinetics

A
- Absorbed extensively in the GI, transdermally, or vaginally
- % bioavailability depends on route

D
- Distributed throughout the body
- Concentrates where estrogen receptors are found

M
- Extensive first-pass metabolism (95%) when taken orally
- Interconverts with E1 and conjugates to form estrogen "reservoir"
- Partial elimination by CYP3A4

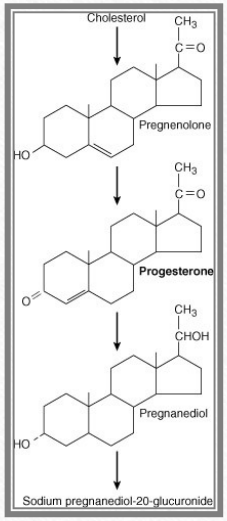
E
- Primarily renal elimination
- Some biliary recirculation
- Half-life depends on formulation

Estrogen Distribution

- The distribution of exogenous estrogens is similar to that of endogenous estrogens
- Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs
- Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin

Biosynthesis of Progesterone

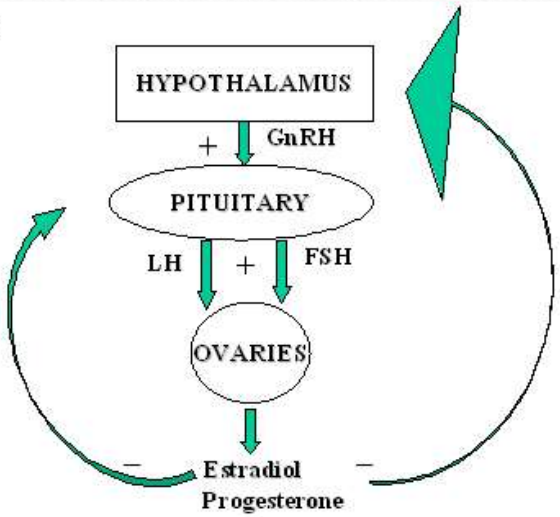
- Progesterone is a C_{21} steroid secreted by the corpus luteum, the placenta, and in small amounts by the follicle
- It is an important intermediate in steroid biosynthesis in all tissues that secrete steroid hormones, and small amounts enter the circulation from the testes and adrenal cortex
- 2% of circulating progesterone is free whereas 80% is bound to albumin and 18% bound to corticosteroid-binding globulin
- Progesterone has a short half-life and is converted in the liver to pregnanediol, which is conjugated to glucuronic acid and excreted in the urine



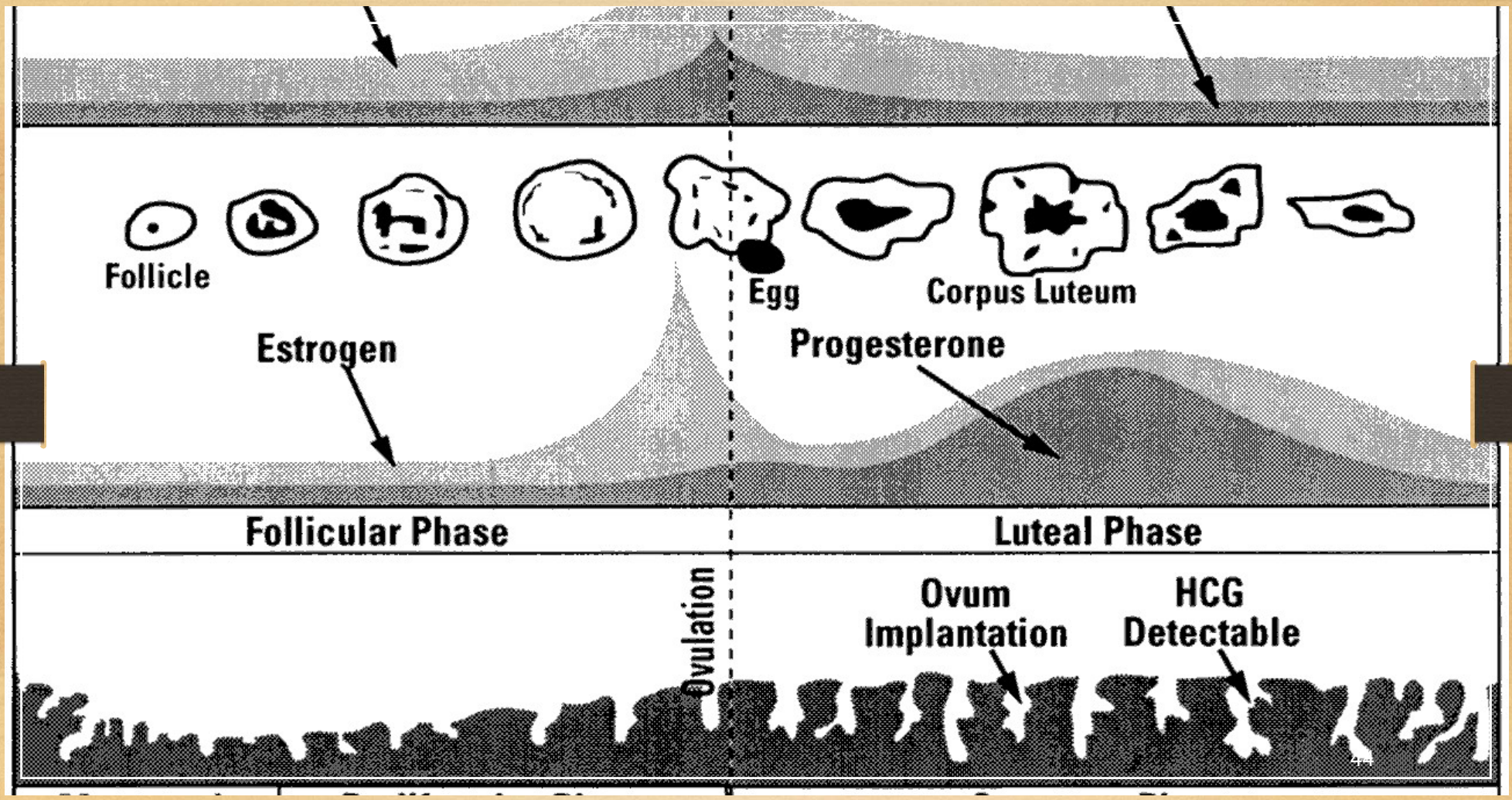
Secretion of Progesterone

- In men, plasma progesterone level is approximately 0.3 ng/ml (1 nmol/L)
- In women, the level is approximately 0.9 ng/ml (3 nmol/L) during the follicular phase of the menstrual cycle
  - Difference is due to the small amounts of progesterone by cells in the ovarian follicles; theca cells provide pregnenolone to the granulosa cells, which convert it to progesterone

Figure 1

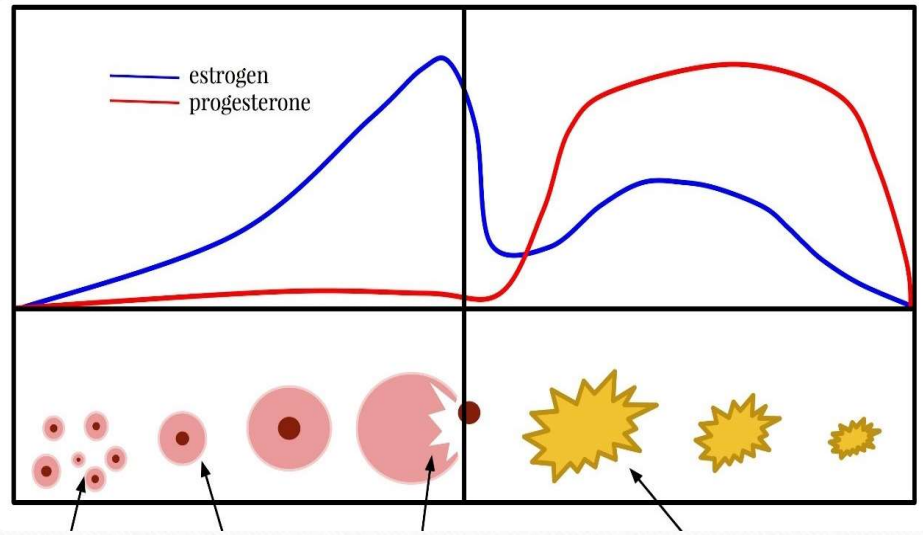


Barrett KE, BBarman SM, Boitano S, Brooks HL. "Chapter 25. The Gonads: Development & Function of the Reproductive system" Ganong's Review of Medical Physiology. 23rd Ed. The McGraw-Hills Co., 2010


Follicle
Egg
Corpus Luteum
Estrogen
Progesterone
Follicular Phase
Luteal Phase
Ovulation
Ovum Implantation
HCG Detectable

Secretion of Progesterone

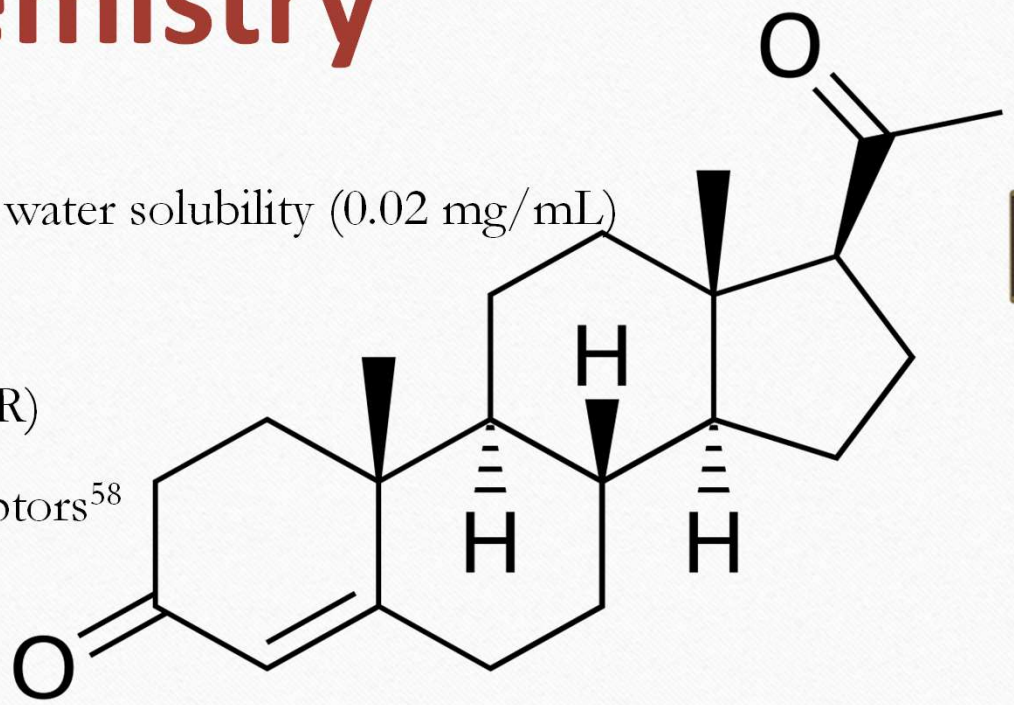
- Late in the follicular phase, progesterone secretion begins to increase
- During luteal phase, the corpus luteum produces large quantities of progesterone and plasma progesterone is markedly increased to a peak value of approximately 18 ng/ml (60 nmol/L)



Barrett KE, BBarman SM, Boitano S, Brooks HL. "Chapter 25. The Gonads: Development & Function of the Reproductive system" Ganong's Review of Medical Physiology. 23rd Ed. The McGraw-Hills Co., 2010

Progesterone Chemistry

- Progesterone is nonpolar with poor water solubility (0.02 mg/mL)
- It is lipophilic: logPoct/water = 3.9
- Activates progesterone receptors (PR)
- Allosteric activator of GABA resceptors[58]



Progesterone Pharmacokinetics

A

- Absorbed extensively in the GI or vaginally
- % bioavailability depends on route - <10% oral
- POOR transdermal absorption

D

- Highly protein bound
- Can cross the blood-brain barrier

M

- Extensive by the intestines and liver, primarily by 5α-reductase
- Over 30 different circulating metabolites

E

- Renal and biliary elimination
- Half-life depends on formulation – ranges from minutes to days

Progesterone Effects

Progesterone binds to two forms of receptors: PRA and PRB

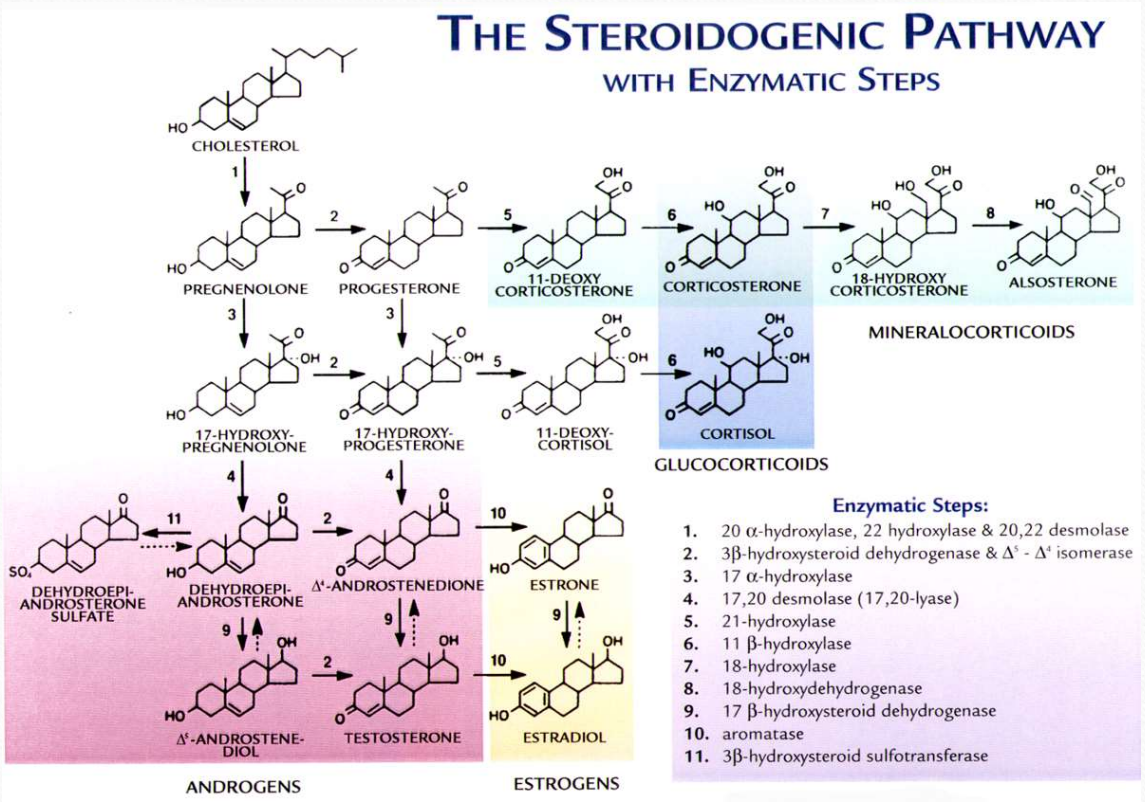
Regulate reproductive function when PRA/B expressed in:

Uterus, ovaries, mammary gland, and brain

Also plays important roles in maintaining function in non-reproductive systems:

Cardiovascular system, bone, central nervous system

THE STEROIDOGENIC PATHWAY
WITH ENZYMATIC STEPS



Enzymatic Steps:

1. 20 α-hydroxylase, 22 hydroxylase & 20,22 desmolase
2. 3β-hydroxysteroid dehydrogenase & Δ^5 - Δ^4 isomerase
3. 17 α-hydroxylase
4. 17,20 desmolase (17,20-lyase)
5. 21-hydroxylase
6. 11 β-hydroxylase
7. 18-hydroxylase
8. 18-hydroxydehydrogenase
9. 17 β-hydroxysteroid dehydrogenase
10. aromatase
11. 3β-hydroxysteroid sulfotransferase

Effects of Progesterone

- Principal target organs of progesterone are the uterus, the breasts, and the brain
- Progesterone has an antiestrogenic effect on the myometrial cells, decreasing their excitability, their sensitivity to oxytocin, and their spontaneous electrical activity while increasing their membrane potential
- It downregulates the number of estrogen receptors in the endometrium and increases the rate of conversion of 17β-estradiol to less active estrogens

Progestin
Excess
Acne
Increased appetite/weight gain
Fatigue
Hypertension
Depression
Hirsutism
Vaginal yeast infections
Deficiency
Late breakthrough bleeding
Amenorrhea
Heavy menstrual flow

Effect of Progesterone

- Large doses of progesterone inhibits LH secretion and potentiate the inhibitory effect of estrogens, preventing ovulation
- Progesterone is thermogenic and may be responsible for the rise in basal body temperature at the time of ovulation
- Large doses of progesterone produces natriuresis by blocking the action of aldosterone in the kidney
- It does not have significant anabolic effect

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Heavy menstrual flow

Transdermal Progesterone

- Transdermal progesterone (40 mg per day) increased serum progesterone to a small extent (mean Cmax after 42 days of use, 5.3 nmol/L).
- The achieved serum levels of progesterone are lower than those achieved with vaginal progesterone gel or oral micronized progesterone at doses sufficient to induce secretory transformation of endometrium.

Carey BJ, Carey AH, Patel S, et al: A study to evaluate serum and urinary hormone levels following short and long term administration of two regimens of progesterone cream in postmenopausal women. Br J Obstet Gynaecol 2000; 107:722-726.

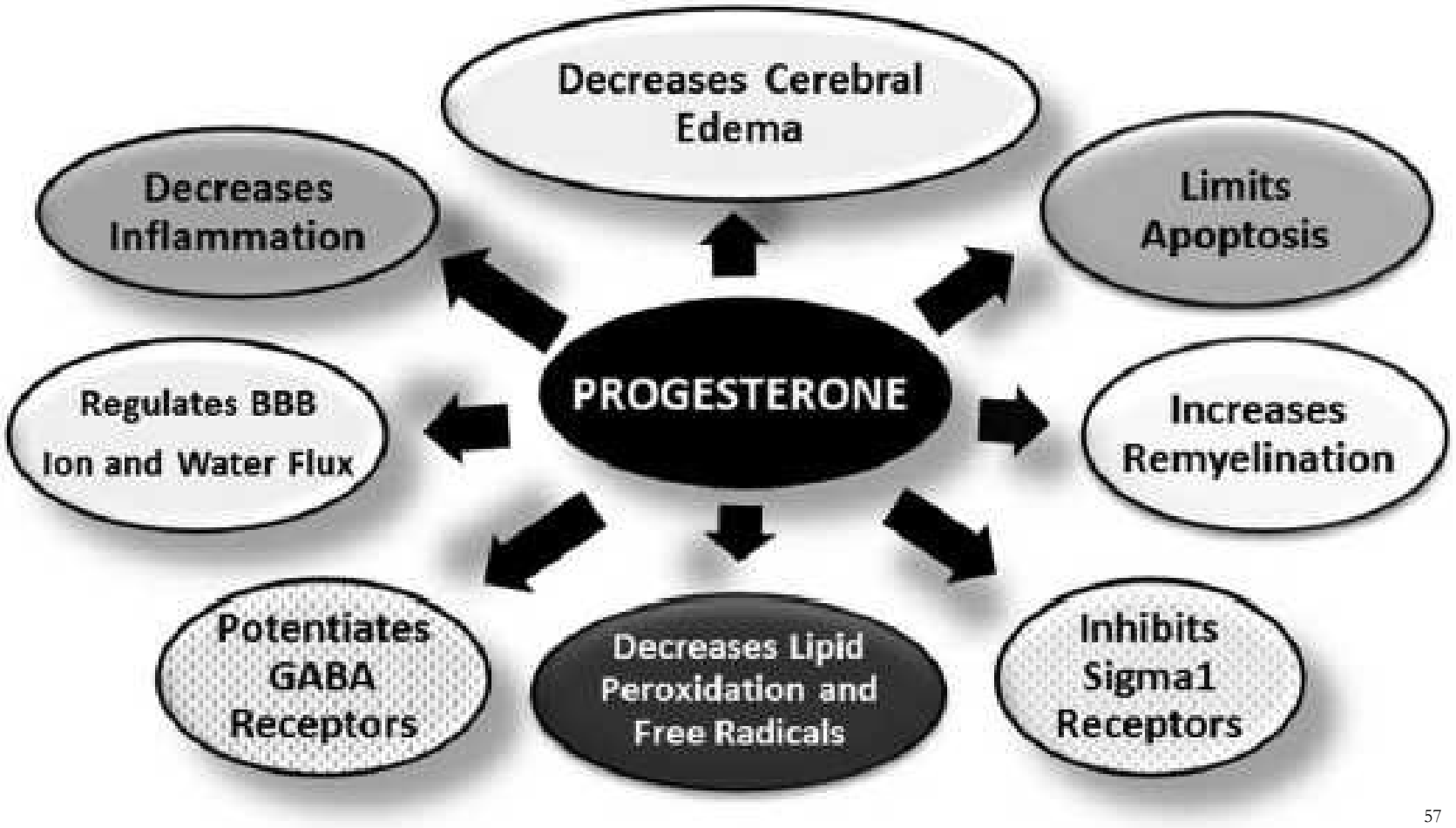
Caution with Transdermal Progesterone

TRANSDERMAL PROGESTERONE			
Leonetti, et. al. 2005	0.625 mg / day conjugated equine estrogens	2.5 mg medroxyprogesterone acetate (MPA) followed by 20 mg transdermal progesterone or vice versa	yes
Vashisht, et. al. 2005	1 mg / day transdermal estradiol	40 mg transdermal progesterone	no
Wren, et. al. 2000	100 mcg estradiol patch	16 mg, 32 mg, or 64 mg transdermal progesterone	no (even if saliva Pg high)

Route of Progesterone-Endometrial Protection

- Based on a systematic literature review on micronized progesterone for endometrial protection, an international expert panel's recommendations on MHT containing micronized progesterone are as follows:
  - oral micronized progesterone provides endometrial protection if applied sequentially for 12-14 days/month at 200 mg/day for up to 5 years
  - vaginal micronized progesterone may provide endometrial protection if applied sequentially for at least 10 days/month at 4% (45 mg/day) or every other day at 100 mg/day for up to 3-5 years (off-label use)
  - transdermal micronized progesterone does not provide endometrial protection.

Climacteric 2016 Aug;19(4):316-28



Neuroprotection of Progesterone

- Progesterone has been reported to exert protective effects on brain dysfunction seen with advanced age- or age-related neurodegenerative diseases such as Alzheimer's Disease
- Shown to attenuate oxidative injury resulting from glutamate and glucose deprivation-induced toxicity
- Protects against FeSO4 and amyloid B-peptide-induced toxicity in primary hippocampal cultures

Horm Behav. 2013;63(2):284-290.
Acta Pharmacologica Sinica. 2013; 34:1485-1490.

Neuroprotection of Progesterone

- In traumatic brain injury, progesterone reduces cerebral edema for up to 24 hours after injury
- Beneficial effect on spinal cord contusion injuries
  - Progesterone reduces the size of the lesion and prevents secondary neuronal loss
- Controversial if progesterone interferes with the beneficial effects of estrogen

Horm Behav. 2013;63(2):284-290.
Acta Pharmacologica Sinica. 2013; 34:1485-1490.

Neuroprotection of Progesterone

- Mechanisms
  - Regulation of neurotrophin expression, which promotes cell survival
  - Novel receptor system – membrane PR or the sigma receptor to activate certain signal transduction pathways and triggers cellular events
  - Major metabolites of progesterone such as allopregnanolone contribute to the neuroprotective effects of progesterone

Horm Behav. 2013;63(2):284-290.
Acta Pharmacologica Sinica. 2013; 34:1485-1490.

Breast Cancer

- Effect of HT on breast cancer risk may depend on the type of HT, dose, duration of use, regimen, route of administration, prior exposure, and individual characteristics
  - WHI results suggest a nonsignificant reduced risk of breast cancer with CEE alone in women with a hysterectomy
  - Similar nonsignificant reductions for estradiol were observed in two smaller randomized trials (approx 1,000 perimenopausal and postmenopausal participants), although not in all large observational studies

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause: The Journal of The North American Menopause Society*. 2017;24(7):728-753.

Breast Cancer

- Effect of HT on breast cancer risk may depend on the type of HT, dose, duration of use, regimen, route of administration, prior exposure, and individual characteristics
  - Rare absolute risk of breast cancer (< 1 additional case/1,000 person-years of use) was seen with daily continuous-combined CEE + MPA in the WHI but not seen in all trials or all subanalyses of the WHI, such as in women without prior HT exposure, but it is consistent with many observational trial results
  - The potential risk of breast cancer should be included in discussions about benefits and risks of HT

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause: The Journal of The North American Menopause Society*. 2017;24(7):728-753.

Breast Cancer

- Duration of HT use may be an important factor in breast cancer risk, because in some studies, risk increased with longer durations of use
- Different HT regimens may be associated with increased breast density, which may be obscure mammographic interpretation, leading to more mammograms or more breast biopsies
- In trials up to 2-years' duration, breast tenderness, breast density, and breast cancers were not increased with oral CEE plus bazedoxifene compared with placebo
- Limited observational evidence suggests that HT use does not further increase risk of breast cancer in women with a family history of breast cancer or in women after oophorectomy for *BRCA 1 or 2* gene mutation

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause: The Journal of The North American Menopause Society*. 2017;24(7):728-753.

Breast Cancer

- Systemic HT is not recommended for survivors of breast cancer, although selected cases with compelling reasons may be discussed in conjunction with an oncologist after non-hormone options have been unsuccessful
- For survivors of breast cancer with bothersome GSM symptoms, low-dose vaginal ET, with minimal systemic absorption, may be considered after a failed trial of non-hormone therapies and in consultation with an oncologist
  - There is a concern even with low-dose vaginal ET for women on Ais because of suppressed estradiol levels

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause: The Journal of The North American Menopause Society*. 2017;24(7):728-753.

Breast Cancer

- Progesterone and synthetic progestins have similar effects on endometrial tissue but there is significant evidence that they have differing effects on breast tissue proliferation
- Synthetic progestins have clear association with increased risk for breast cancer
  - Women's Health Initiative: MPA significantly increased risk for breast cancer (RR=1.26; CI: 1.00-1.59)
  - Lyytinen et al: combination estrogen and progestogen increases risk of breast cancer after 3 years ($P<0.05$)

Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003;289(24):3243-3253
Lyytinen H, Pukkala E, Ylikorkala O, et al. Breast cancer risk in postmenopausal women using estradiol-progestogen therapy. Obstetrics & Gynecology 2009;113(1):65-73
Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med 1995;332(24):1589-1593
Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J Natl Cancer Inst 2000;92(4):328-332

Breast Cancer (Cont.)

- Synthetic progestins have clear association with increased risk for breast cancer
  - Rose et al: compared risk for breast cancer in 1897 women on estrogen and synthetic progestin v. 1637 control patients who had never used HRT
    - Synthetic progestin increased risk for breast cancer by 25% for each 5 years of use compared with estrogen alone (RR=1.25; CI: 1.02-1.18)

Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003;289(24):3243-3253
Lyytinen H, Pukkala E, Ylikorkala O, et al. Breast cancer risk in postmenopausal women using estradiol-progestogen therapy. Obstetrics & Gynecology 2009;113(1):65-73
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Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J Natl Cancer Inst 2000;92(4):328-332

Breast Cancer (Cont.)

- Synthetic progestins have clear association with increased risk for breast cancer
  - Nurses' Health Study: 58,000 postmenopausal women were followed for 16 years (725,000 women-years)
    - Unopposed estrogen use increased risk for breast cancer by 23% (CI: 6-42) but addition of synthetic progestin resulted in tripling of risk (67% increased risk; CI: 18-136)

Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003;289(24):3243-3253
Lyytinen H, Pukkala E, Ylikorkala O, et al. Breast cancer risk in postmenopausal women using estradiol-progestogen therapy. Obstetrics & Gynecology 2009;113(1):65-73
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Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J Natl Cancer Inst 2000;92(4):328-332

Risk of Breast Cancer with Synthetic Progestin cont.

- Lee et al: meta-analysis of 61 studies
  - Found consistently increased risk for breast cancer with synthetic HRT with average increase of 7.6% per year of use (CI: 1.070-1.082) and higher dose of synthetic progestin conferred a significantly increased risk for breast cancer

Lee SA, Ross RK, Pike MC. An overview of menopausal oestrogen-progestin hormone therapy and breast cancer risk. Br J Cancer 2005;92(11):2049-2058
Ewertz M, Mellemkjaer L, Poulsen AH, et al. Hormone use for menopausal symptoms and risk of breast cancer. A Danish Cohort study. Br J Cancer 2005;92(7):1293-1297
Chlebowski, Rowan T. et al. "Estrogen plus Progestin and Breast Cancer Incidence and Mortality in Postmenopausal Women." *JAMA* 304.15 (2010): 1684–1692. *PMC*. Web. 11 June 2018.

Risk of Breast Cancer with Synthetic Progestin cont.

- Ewertz et al: analyzed risk for breast cancer for 80,000 women from 1989-2002
  - Women older than 50 years using HRT had a 61% increased risk for breast cancer (CI: 1.38-1.88) and longer duration of use and use of synthetic progestins derived from testosterone were associated with increased risk

Lee SA, Ross RK, Pike MC. An overview of menopausal oestrogen-progestin hormone therapy and breast cancer risk. Br J Cancer 2005;92(11):2049-2058
Ewertz M, Mellemkjaer L, Poulsen AH, et al. Hormone use for menopausal symptoms and risk of breast cancer. A Danish Cohort study. Br J Cancer 2005;92(7):1293-1297
Chlebowski, Rowan T. et al. "Estrogen plus Progestin and Breast Cancer Incidence and Mortality in Postmenopausal Women." *JAMA* 304.15 (2010): 1684–1692. *PMC*. Web. 11 June 2018.

Risk of Breast Cancer with Synthetic Progestin cont.

- Chlebowski et al: examined risk for breast cancer with synthetic HRT (0.625 mg/day CEE; 2.5 mg/day MPA) in 16,608 postmenopausal women
  - Estrogen plus progestin increased invasive breast cancers compared with placebo (385 [0.42%/yr] vs 293 [0.34%/yr] cases; hazard ratio [HR] 1.25, 95% confidence interval (CI) 1.07-1.46; P=.004).
  - Deaths directly attributed to breast cancer were greater in the estrogen plus progestin group (25 [0.03%/yr] vs 12 [0.01%/yr] deaths; HR, 1.96; 95% CI 1.00-4.04, P=.049) as were deaths from all causes occurring after a breast cancer diagnosis (51 [0.05%/yr] vs 31 [0.03%/yr] deaths; HR 1.57, 95% CI 1.01-2.48; P=.045).

Lee SA, Ross RK, Pike MC. An overview of menopausal oestrogen-progestin hormone therapy and breast cancer risk. Br J Cancer 2005;92(11):2049-2058
Ewertz M, Mellemkjaer L, Poulsen AH, et al. Hormone use for menopausal symptoms and risk of breast cancer. A Danish Cohort study. Br J Cancer 2005;92(7):1293-1297
Chlebowski, Rowan T. et al. "Estrogen plus Progestin and Breast Cancer Incidence and Mortality in Postmenopausal Women." *JAMA* 304.15 (2010): 1684–1692. *PMC*. Web. 11 June 2018.

Risk of Breast Cancer with Bioidentical Progesterone

- Progesterone shown to decrease risk for breast cancer
  - Fourier et al: reported association between various forms of HRT and incidence of breast cancer in 80,000 postmenopausal women followed for > 8 years
    - Estrogen-only had non-significant increase of 1.29 times risk (P=0.73) but if synthetic progestin added to combination, risk increases to 1.69 times control (P=0.01)
    - Combination progesterone and estrogen significantly reduced risk compared with synthetic progestin (P=0.001)

Fournier A, Berrino F, Clave-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat 2008;107(1):103-111
Fournier A, Berrino F, Riboli E, et al. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int J Cancer 2005;114:448-545
Wood CE, Register TC, Lees CJ, et al. Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys. Breast Cancer Res Treat 2007;101(2):125-134

Risk of Breast Cancer with Bioidentical Progesterone

- Progesterone shown to decrease risk for breast cancer
  - Fourier et al: in another study of 50,000 postmenopausal women
    - Risk significantly increased if synthetic progestin used (RR=1.4) but was reduced if progesterone was used (RR=0.9)
    - Significant difference in risk for breast cancer between use of estrogens combined with synthetic progestins v. estrogens combined with progesterone ($P<0.001$)

Fournier A, Berrino F, Clave-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat 2008;107(1):103-111
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Risk of Breast Cancer with Bioidentical Progesterone

- Progesterone shown to decrease risk for breast cancer
  - Wood et al: post-menopausal primate given placebo, estradiol, estradiol + MPA, estradiol + progesterone for 2 months with 1-month washout period
    - Compared with placebo, significantly increased proliferation found with combination of estrogen + MPA in both lobular (P=0.009) and ductal tissues (P=0.006), but was not seen with estrogen + progesterone

Fournier A, Berrino F, Clave-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat 2008;107(1):103-111
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  - Wood et al: post-menopausal primate given placebo, estradiol, estradiol + MPA, estradiol + progesterone for 2 months with 1-month washout period
    - Intramammary gene expressions of proliferation markers were also higher after treatment with estrogen + MPA (4.9-fold increase P=0.007; 4.3-fold increase P=0.002), but not with estrogen + progesterone

Fournier A, Berrino F, Clave-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat 2008;107(1):103-111
Fournier A, Berrino F, Riboli E, et al. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int J Cancer 2005;114:448-545
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Risk of Breast Cancer with Bioidentical Progesterone

- Chang et al: double-blind, placebo-controlled study of estrogen and progesterone on women prior to breast surgery given placebo, estrogen, transdermal progesterone, or estrogen + transdermal progesterone for 10-13 days prior to surgery
  - Estrogen increased cell proliferation rates by 230% ($P<0.05$) but progesterone decreased cell proliferation rates by 400% ($P<0.05$)

Chang KJ, Lee TY, Linarez-Cruz G, Fournier S, et al. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. Fertil Steril 1995;63(4):785-791
Foidart JM, Colin C, Denoo X, et al. estradiol and progesterone regulate the proliferation of human breast epithelial cells. Fertil Steril 1998;69(5):963-969
Cowan LD, Gordis L, Tonascia JA, Jones GS. Breast cancer incidence in women with a history of progesterone deficiency. Am J Epidemiol 1981;114(2):209-217
Micheli A, Muti P, Secreto G, et al. Endogenous sex hormones and subsequent breast cancer in premenopausal women. Int J Cancer 2004;112(2):312-318
Peck JD, Hulka BS, Poole C, et al. Steroid hormone levels during pregnancy and incidence of maternal breast cancer. Cancer Epidemiol Biomarkers Prev 2002;11(4):361-368

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  - Progesterone given with estradiol inhibited estrogen-induced breast cell proliferation

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Risk of Breast Cancer with Bioidentical Progesterone

- Foidart et al: randomized, double-blind study
  - Progesterone eliminated estrogen-induced breast cell proliferation (P=0.001)

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Risk of Breast Cancer with Bioidentical Progesterone

- Cowan et al: epidemiological study of 1083 women treated for infertility, followed for 13-33 years
  - Premenopausal risk for breast cancer was 5.4 times higher in women with low progesterone levels compared to those with normal (CI: 1.1-49)
  - There were 10 times as many deaths from cancer in low progesterone group compared with those with normal progesterone levels (CI: 1.3-422)

Chang KJ, Lee TY, Linarez-Cruz G, Fournier S, et al. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. Fertil Steril 1995;63(4):785-791
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Risk of Breast Cancer with Bioidentical Progesterone

- Micheli et al: Prospective study of luteal phase progesterone levels in 5963 women and assessment of risks for breast cancer
  - Progesterone was inversely associated with breast cancer risk (RR=0.40; CI: 0.15-1.08m P for trend=0.077)

Chang KJ, Lee TY, Linarez-Cruz G, Fournier S, et al. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. Fertil Steril 1995;63(4):785-791
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Peck JD, Hulka BS, Poole C, et al. Steroid hormone levels during pregnancy and incidence of maternal breast cancer. Cancer Epidemiol Biomarkers Prev 2002;11(4):361-368

Risk of Breast Cancer with Bioidentical Progesterone

- Peck et al: nested case-control study examining third-trimester progesterone levels and maternal risk of breast cancer
  - Increasing progesterone levels were associated with a decreased risk of breast cancer

Chang KJ, Lee TY, Linarez-Cruz G, Fournier S, et al. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. Fertil Steril 1995;63(4):785-791
Foidart JM, Colin C, Denoo X, et al. estradiol and progesterone regulate the proliferation of human breast epithelial cells. Fertil Steril 1998;69(5):963-969
Cowan LD, Gordis L, Tonascia JA, Jones GS. Breast cancer incidence in women with a history of progesterone deficiency. Am J Epidemiol 1981;114(2):209-217
Micheli A, Muti P, Secreto G, et al. Endogenous sex hormones and subsequent breast cancer in premenopausal women. Int J Cancer 2004;112(2):312-318
Peck JD, Hulka BS, Poole C, et al. Steroid hormone levels during pregnancy and incidence of maternal breast cancer. Cancer Epidemiol Biomarkers Prev 2002;11(4):361-368

Risk of Breast Cancer with Bioidentical Progesterone

- Peck et al: nested case-control study examining third-trimester progesterone levels and maternal risk of breast cancer
  - Relative to those with progesterone levels in lowest quartile (<124.25ng/mL), those in highest quartile (>269.97ng/mL) had a 50% reduction in incidence of breast cancer (RR=0.49; CI:0.22-1.1, P for trend=0.08)

Chang KJ, Lee TY, Linarez-Cruz G, Fournier S, et al. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. Fertil Steril 1995;63(4):785-791
Foidart JM, Colin C, Denoo X, et al. estradiol and progesterone regulate the proliferation of human breast epithelial cells. Fertil Steril 1998;69(5):963-969
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Peck JD, Hulka BS, Poole C, et al. Steroid hormone levels during pregnancy and incidence of maternal breast cancer. Cancer Epidemiol Biomarkers Prev 2002;11(4):361-368

Risk of Breast Cancer with Bioidentical Progesterone

- Peck et al: nested case-control study examining third-trimester progesterone levels and maternal risk of breast cancer
  - Association was stronger for cancers diagnosed at or before age of 50 (RR=0.3; CI:0.1-0.9, P for trend=0.04)

Chang KJ, Lee TY, Linarez-Cruz G, Fournier S, et al. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. Fertil Steril 1995;63(4):785-791
Foidart JM, Colin C, Denoo X, et al. estradiol and progesterone regulate the proliferation of human breast epithelial cells. Fertil Steril 1998;69(5):963-969
Cowan LD, Gordis L, Tonascia JA, Jones GS. Breast cancer incidence in women with a history of progesterone deficiency. Am J Epidemiol 1981;114(2):209-217
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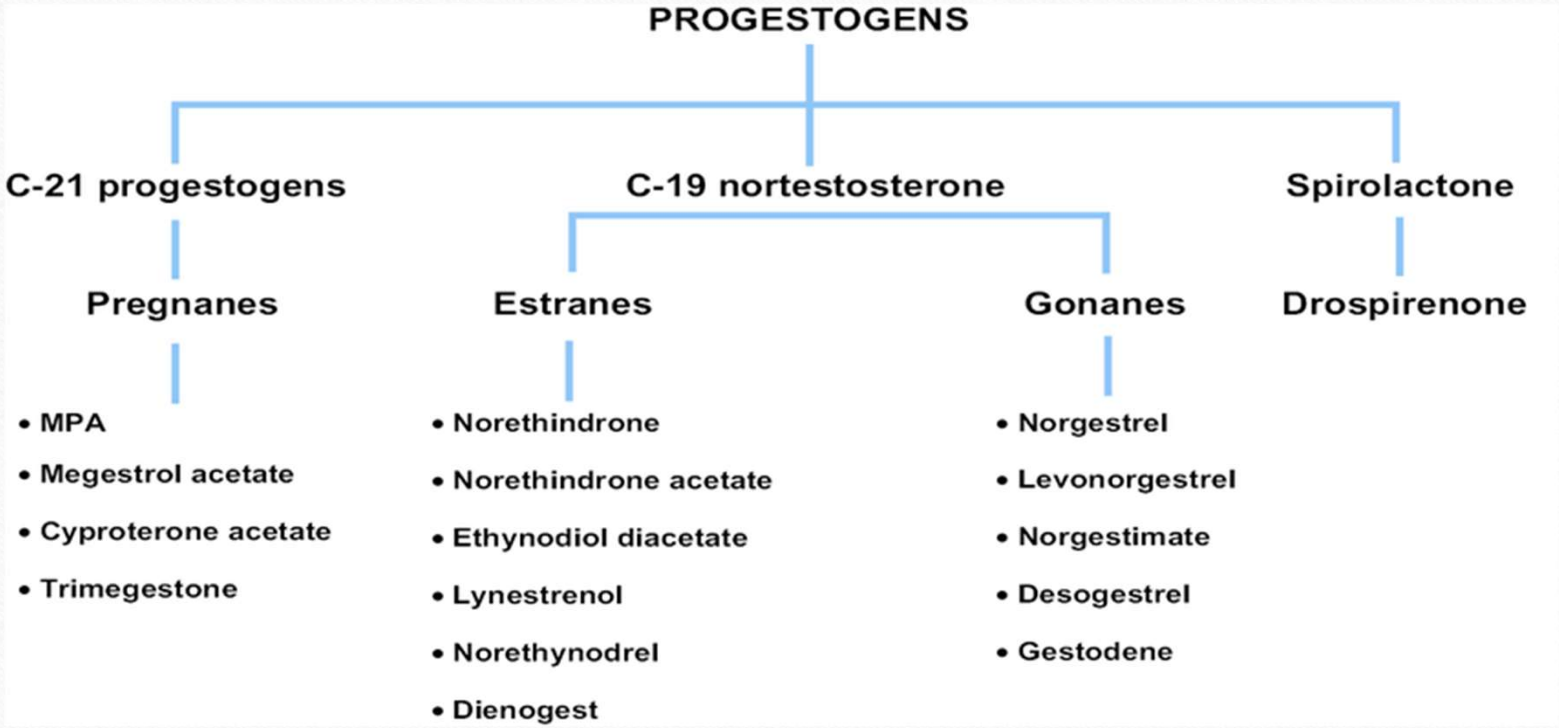
Progestogens

- Synthetic forms of progesterone
- Developed as a result of inability of progesterone to be absorbed orally
- Classification of Synthetic progestogens
  - ✓ **Progesterone analogues:** Dydrogesterone.
  - ✓ **17-OH progesterone group:** medroxyprogesterone acetate and cyproterone acetate.
  - ✓ **19-nor progesterone group:** nomegestrol acetate (NOMAC), trimegestone, promegestone.
  - ✓ **Estranes:** norethisterone
  - ✓ **Estrane/pregnane:** dienogest
  - ✓ **Gonanes:** norgestrel and levonorgestrel (the active isomer of norgestrel), desogestrel, norgestimate and gestodene
- Progesterone analogues are less androgenic than the testosterone analogues [21].

APGAR BS. Using Progestins in Clinical Practice. Am Fam Physician. 2000;62(8):1839-1846

Synthesis of Progestogens



Progestogens

Oral

Provera - medroxyprogesterone

- Absorption:
  - Rapidly absorbed from GI tract
  - Cmax is dose dependent (food increases Cmax by 50-70%)
- Distribution:
  - Highly protein bound (primarily albumin)
  - No SHBG binding
- Metabolism:
  - Extensive hepatic metabolism via hydroxylation
- Elimination:
  - T½ = 40-60hrs
  - Excreted via urine as glucuronide conjugates

*More potent than progesterone

Johansson ED, Johansen PB, Rasmussen SN. Medroxyprogesterone acetate pharmacokinetics following oral high-dose administration in humans: a bioavailability evaluation of a new MPA tablet formulation. *Acta Pharmacol Toxicol (Copenh)*. 1986;58(5):311-317. doi:10.1111/j.1600-0773.1986.tb00115.x

"Medroxyprogesterone Acetate." *Uses, Interactions, Mechanism of Action | DrugBank Online*, 13 June 2005, https://go.drugbank.com/drugs/DB00603.

Oral

Prometrium - progesterone

- Absorption:
  - Rapidly absorbed from GI tract (peaks within 3 hrs)
  - Cmax is dose dependent (food increases Cmax by 50-70%)
  - Bioavailablility 10-15%
- Distribution:
  - Highly protein bound (primarily albumin)
  - No SHBG binding

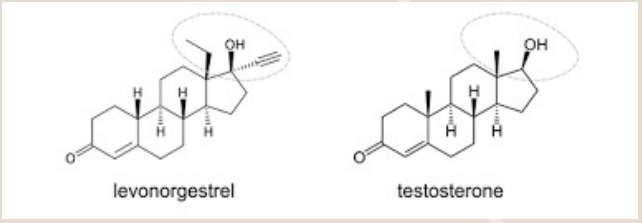
rate

- Metabolism:
  - Extensive hepatic metabolism via dehydroxylation and reduction
- Elimination:
  - T½ = ~1hr
  - Excreted via urine (50-60%) as glucuronide conjugates

*Poor bioavailability, rapid clearance

Progesterone vs Progestins

Progesterone	Medroxyprogesterone, norethindrone, levonorgestrel, norgestimate, etc.
Anti-androgenic	Androgenic activity (varies by agent)
Hair growth	Hair loss / follicle shrinkage (varies by agent)
Increased BMD	Decreased BMD
Cardioprotective	May increase risk of CV events
Neuroprotective	Potential cognitive decline

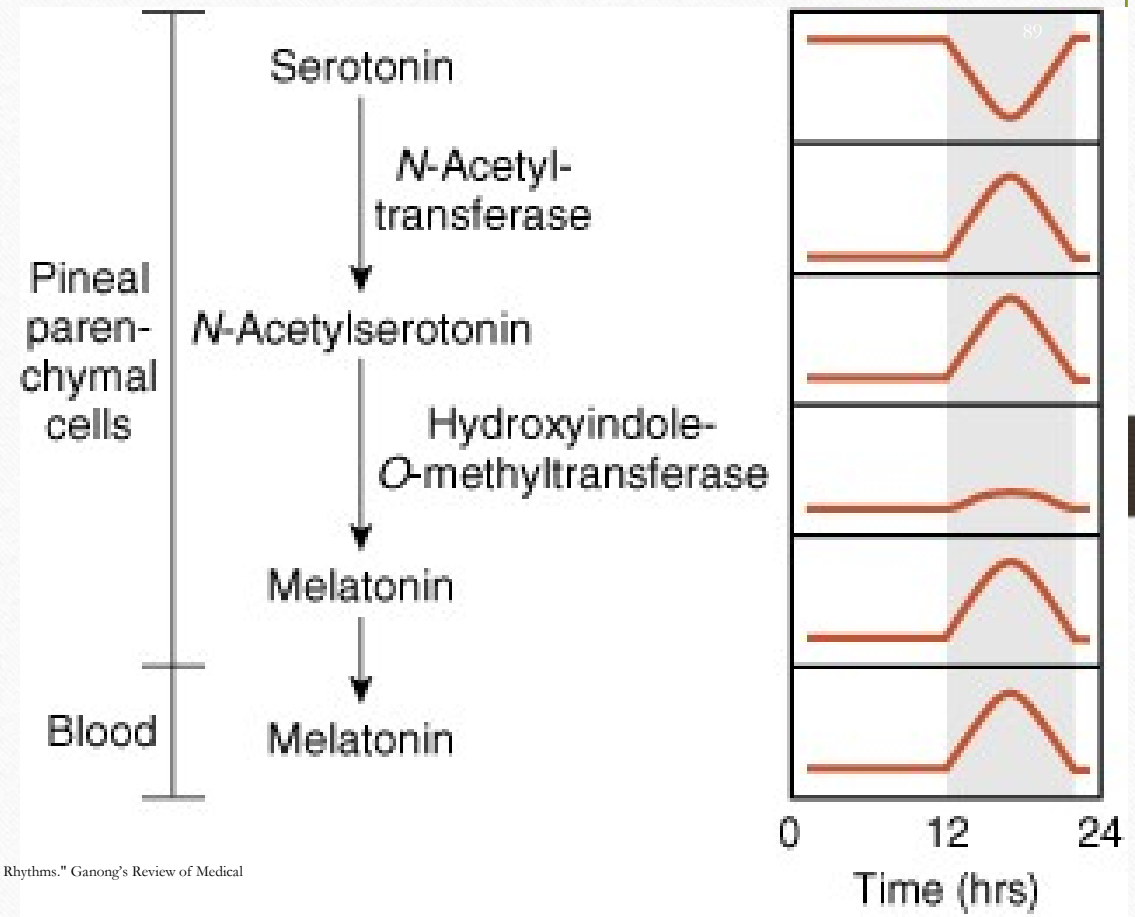


(Guennoun, 2020)
(Gava, 2020)
(Thomas, 2020)

(Seifert-Klauss, 2010)
(Shumaker, 2003)

Melatonin and the Sleep-Wake State

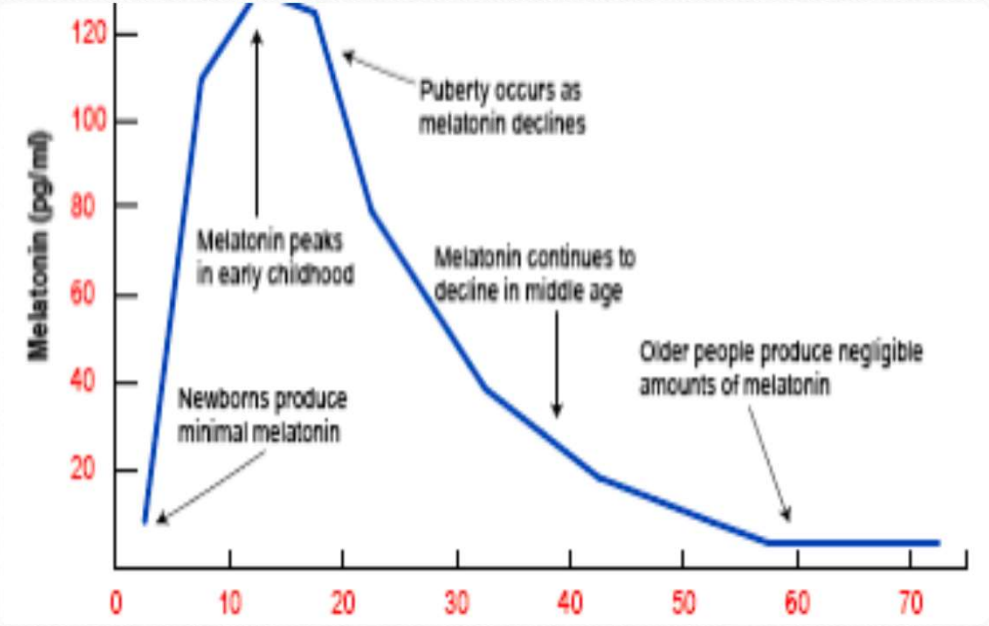
- Release from the richly vascularized pineal gland
- Plays a role in sleep mechanisms
- Melatonin and intermediate enzymes responsible for its synthesis from precursor serotonin, by N-acetylation and O-methylation are present in pineal pinealocytes
- Secreted into the blood and the cerebrospinal fluid
- Synthesis and secretion are increased during the dark period of the day and maintained at a low level during daylight hours



Barrett KE, BBarman SM, Boitano S, Brooks HL. "Chapter 15. Electrical Activity of the Brain, Sleep-Wake States, & Circadian Rhythms." Ganong's Review of Medical Physiology. 23rd Ed. The McGraw-Hills Co., 2010

Melatonin and the Sleep-Wake State

- The diurnal variation in secretion is brought about by norepinephrine
- Circulating melatonin is rapidly metabolized in the liver by 6-hydroxylation followed by conjugation
- Over 90% of melatonin that appears in the urine is in the form of 6-hydroxy conjugates and 6-sulfatoxymelatonin



Barrett KE, BBarman SM, Boitano S, Brooks HL. "Chapter 15. Electrical Activity of the Brain, Sleep-Wake States, & Circadian Rhythms." Ganong's Review of Medical Physiology. 23rd Ed. The McGraw-Hills Co., 2010

Pregnenolone

- Synthesized directly from cholesterol
  - Precursor to all other sex hormones
- Levels start to decline around age 30
- Functions to:
  - Enhance nerve transmission and memory
  - Improve energy and sleep
  - Increase stress resistance
  - Mood elevation
  - Reduce pain and inflammation
- Deficiency associated with:
  - Depression
  - Fatigue
  - Inability to deal with stress
  - Insomnia
  - Lack of focus
  - Memory decline

Pregnenolone Dosing

- Pregnenolone E4M to start at 10mg per day and titrate up slowly until you reach a blood level of 100 which is optimal
- E4M form more physiological
- Can cause agitation and anxiety if titrate to fast or if the dose is high for patient

DHEA

- Made by the adrenal glands
- Precursor to estrogen and testosterone
- Production declines with age
- Protective effect against:
  - Cancer, diabetes, obesity, high cholesterol, heart disease, and autoimmune diseases
- Symptoms of deficiency:
  - Decreased energy & muscle strength, difficulty dealing with stress, increase risk of infection, irritabilty, joint soreness, and weight gain

DHEA Dosing

- Women 2.5-7mg per day
- Men need 25-50mg per day
- E4M form is more physiological
- DHEA is a large molecule and therefore, it is not well absorbed topically
- Side effects include oily skin, hirsutism, acne
- K-DHEA form can be used if concern for cancer and want to bypass hormonal byproducts

Intrarosa (prasterone)

- Absorption:
  - Inactive precursor (requires conversion into active testosterone and estradiol)
- Distribution:
  - Mainly local intravaginal (some increase in systemic exposure observed)

*Adverse Effects: vaginal discharge (≥2%), abnormal pap smear (atypical cells)

- Metabolism:
  - Hydroxysteroid dehydrogenase, 5a-reductase, and aromatases
- Elimination:
  - T½ = ~12hrs

Intrarosa (prasterone)

- Dosage Form: vaginal insert
- Strength: 6.5mg prasterone in 1.3ml Witepsol
- Only FDA-approved DHEA product
- Serum testosterone levels return to baseline 12hrs post-dose
- Serum prasterone and estradiol levels remained above baseline 24hrs post-dose

	Prasterone	Testosterone	Estradiol
Serum Cavg (over 7 days)	4.42 ng/ml	0.15 ng/ml	5.04 pg/ml
Placebo Cavg (over 7 days)	1.6 ng/ml	0.12 ng/ml	3.33 pg/ml

Intrarosa (prasterone)

- In two primary efficacy trials, daily administration of INTRAROSA vaginal insert for 12 weeks increased mean serum C trough of prasterone and its metabolites testosterone and estradiol by 47%, 21% and 19% from baseline, respectively. This comparison based on C trough may underestimate the magnitude of increase in prasterone and metabolites' exposure because it does not take into account the overall concentration-time profile following administration of INTRAROSA.

	Prasterone	Testosterone	Estradiol
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HRT for Hypoactive Sexual Desire Disorder

Treatments	Routes	Doses	Outcomes	Type of study
Esterified estrogens+ methyltestosterone	Oral	1.25 mg/2.5 mg once/day	No effect of testosterone on either vaginal or fingertip blood flow velocity	A randomized, placebo-controlled trial
Sublingual testosterone undeconate	Sublingual	0.5 mg	increased vaginal blood flow, Self-reported sensations and sexual lust	A double-blind, randomized, placebo-controlled, crossover design
Esterified estrogens alone Estrogen + methyltestosterone	Oral	1.25 mg/day/ 2.5 mg/day	Significant increase in Sexual function	A double-blind, randomized, parallel-group study
DHEA	Intravaginal ovule	0.25%, 0.5%, 1% at bedtime for 3 months	A significant benefit on orgasm for the 1% dose arousal with lubrication Reduced vaginal dryness	Phase III trial

Shufelt CL, Manson JE. Menopausal Hormone Therapy and Cardiovascular Disease: The Role of Formulation, Dose, and Route of Delivery. J Clin Endocrinol Metab. 2021;106(5):1245-1254. doi:10.1210/clinem/dgab042

HRT for Hypoactive Sexual Desire Disorder

Treatment	Route	Doses	Outcomes	Type of study
Testosterone gel [49]	Topical gel	50 mg applied to the abdomen and shoulders 4–8 hours before intercourse up to twice/week for 1 month in 10 premenopausal women	No significant difference was noted for desire, lubrication, orgasm, or satisfaction	Randomized, double-blind, crossover study
Flibanserin [50]		100 mg nightly	Effective in hypoactive sexual desire disorder	Randomized, double-blind, crossover study

Woodis CB, McLendon AN, Muzyk AJ. Testosterone supplementation for hypoactive sexual desire disorder in women. Pharmacotherapy. 2012;32(1):38-53. doi:10.1002/PHAR.1004
Pachano Pesantez GS, Clayton AH. Treatment of Hypoactive Sexual Desire Disorder Among Women: General Considerations and Pharmacological Options. Focus (Am Psychiatr Publ). 2021;19(1):39-45

HRT Doses for Vasomotor Symptoms [39]

Treatments	Doses	Routes
Estradiol	0.025mg/day	Transdermal
Conjugated estrogen/bazedoxifene	0.45 mg/20 mg per day	Oral
Micronized estradiol-17 β	0.5 to 1.0 mg per day	Oral
Estradiol-17 β ring	2 mg per 90-day ring	Vaginal ring
Estradiol acetate	0.05 mg per day	Vaginal ring
Ospemifene	60 mg per day	Oral
Paroxetine	7.5 mg per day	Oral

Hauk L. ACOG Releases Clinical Guidelines on Management of Menopausal Symptoms. Am Fam Physician. 2014;90(5):338-340.

Novel Therapy for Vasomotor Symptoms

Treatment	Type	Mechanism	Doses for trial	Suggested dose
Estetrol (E4) [29]	Natural human fetal estrogen	• Selective action in the tissues and activate nuclear estrogen receptor α (ERα) • Initiate cascade of coregulator activators and repressors • Enhances the effects of endogenous estrogens in the endometrium, vasculature, bone, and vaginal tissues	2 mg to 10 mg over a period of 8 weeks were used	Minimum dose of 15 mg was required to reduce VMS severity

Khan SJ, Kapoor E, Faubion SS, Kling JM. Vasomotor Symptoms During Menopause: A Practical Guide on Current Treatments and Future Perspectives. Int J Womens Health. 2023;15:273-287. Published 2023 Feb 14. doi:10.2147/IJWH.S365808

Other Medications for Menopausal Symptoms

Medication Name	Drug Class	Suggested Dosing
Gabapentin	Gamma-aminobutyric acid (GABA) analogue	100–300mg 3x/day
Paroxetine	SSRI	Paroxetine mesylate: 7.5mg/day Paroxetine HCl: 10–20mg/day
Venlafaxine	SNRI	37.5–150mg/day
Oxybutynin	Anticholinergic, antimuscarinic	2.5mg-5mg/2x daily up to 15mg/day
Clonidine	Antihypertensive; α-2 adrenergic agonist	0.05–0.15mg/day

Khan, S. J., Kapoor, E., Faubion, S. S., & Kling, J. M. (2023). Vasomotor symptoms during menopause: A practical guide on current treatments and future perspectives. *International Journal of Women's Health*, *15*, 273-287. https://doi.org/10.2147/ijwh.s365808

Neurokinin 3 Receptor Antagonists for Menopausal VMS

Drug	Doses	Class	Mechanism of action	Usage
Fezolinetant	30 mg/day and 45 mg/day orally	neurokinin 3 receptor antagonist	• In menopause, VMS (hot flushes) is attributed to an inactivation of the hypothalamic thermoneutral zone due to a decline in estrogen level mainly triggered by altered control mechanisms • CNS network consist of kisspeptin, neurokinin B, and dynorphin (KNDy) neurons located within the hypothalamic preoptic nucleus that activates the neurokinin 3 receptor (NK3R) • Hypertrophy of KNDy neurons involved in regulating body temperature • NK3R antagonists alleviate VMS in postmenopausal women	Hot flush severity was decreased with reduction in frequency of VMS

Gennel A, Stuenkel CA. Neurokinin 3 receptor antagonists for menopausal vasomotor symptoms, an appraisal. Cell Rep Med. 2023;4(6):101076. doi:10.1016/j.xcrm.2023.101076

Take-Aways

1. Replace Hormones as needed and in physiological range
2. Do not use estrogen orally
3. Must monitor and adjust therapy
4. Must review potential risk and benefit for each patient

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- Author, Speaker, and Thought Leader within the areas of Pain Management, Headaches, and HRT
- Board Certified and Advanced Fellow in Anti-Aging and Regenerative Medicine

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Thank You!

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