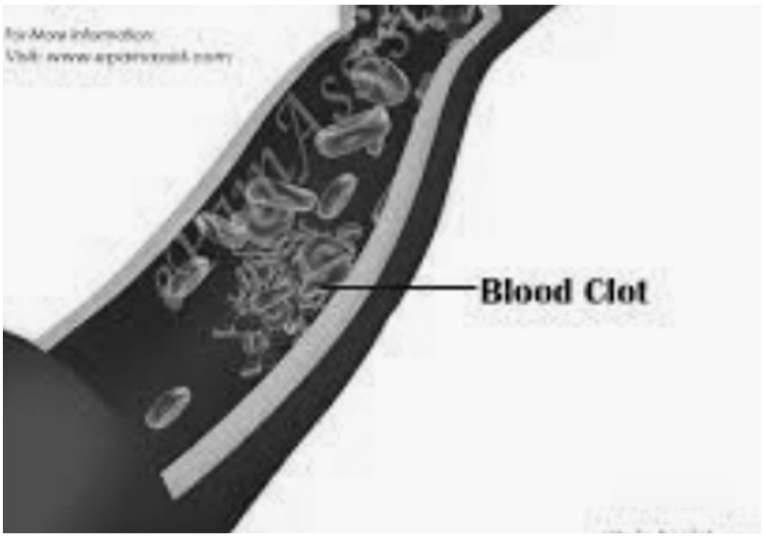
Coagulation genetic diseases: BHRT contraindicated or not

- Need to keep this mind
- And may need to present to other docs or boards
- Not thinking your recommending transdermal BHRT
- To genetic coagulation issue patients is standard of care

1

1

Is Estrogen Coagulable



2

Why Would Mother Nature…

- Make the very molecules that ”drive” humanity
- Hormones
- Be pro-coagulable?

3

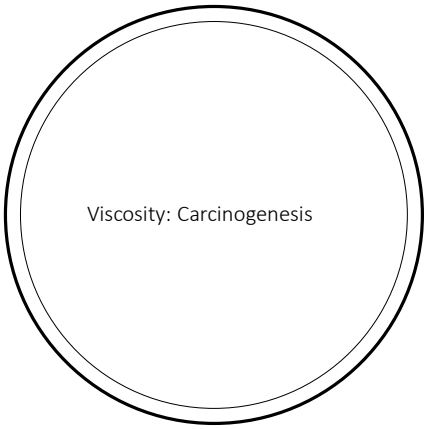
3

Factor V Leiden

- People with factor V Leiden thrombophilia have a higher than average risk of developing a type of blood clot called a deep venous thrombosis (DVT). DVTs occur most often in the legs, although they can also occur in other parts of the body, including the brain, eyes, liver, and kidneys. Factor V Leiden thrombophilia also increases the risk that clots will break away from their original site and travel through the bloodstream. These clots can lodge in the lungs, where
- Although factor V Leiden thrombophilia increases the risk of blood clots, only about 10 percent of individuals with the factor V Leiden mutation ever develop abnormal clots.
- The factor V Leiden mutation is associated with a slightly increased risk of pregnancy loss (miscarriage). Women with this mutation are two to three times more likely to have multiple (recurrent) miscarriages or a pregnancy loss during the second or third trimester. Need more progestereone during pregnancy?

4

4



- The liver is predominantly the place of synthesis of pro-coagulatory clotting factors
- Fibrin is a fibrous, non-globular protein involved in the clotting of blood. It is formed by the action of the protease thrombin on fibrinogen, which causes it to polymerize. The polymerized fibrin, together with platelets, forms a hemostatic plug or clot over a wound site.
- Thrombosis is a major cause of morbidity and mortality in cancer patients.
- Cancer is a hypercoagulable condition.
- **Moreover, venous thromboembolism (VTE) can be the first symptom of an occult malignancy in an otherwise healthy individual**.
-
- **Cancer cells produce and release procoagulant and fibrinolytic proteins, inflammatory cytokines, and procoagulant microparticles**. They also express adhesion molecules binding to the receptors of host vascular cells (i.e., endothelial cells, platelets, and leukocytes), thereby stimulating the prothrombotic properties of these normal cells, including the shed of cell-specific microparticles and neutrophil extracellular traps.
- Transfus Med Hemother. 2009 Dec; 36(6): 419–436. **Procoagulators**

5

Hers & era studies

- Oral contraceptive use in women with factor V Leiden is associated with increased rates of venous thromboembolic events (VTEs). However, the effects of hormone replacement therapy (HRT) in postmenopausal women with factor V Leiden are not known.
- A nested case-control study was conducted among women with established coronary disease enrolled in 2 randomized clinical trials of HRT, **the Heart and Estrogen/Progestin Replacement Study (HERS) and the Estrogen Replacement and Atherosclerosis (ERA) trial.**
- The Leiden mutation was present in 8 (16.7%) of 48 cases with VTE compared with only 7 (6.3%) of 112 controls (odds ratio [OR](Leiden) 3.3, 95% CI 1.1 to 9.8; P=0.03).
- In women without the factor V Leiden mutation, risk associated with HRT use was significantly increased (OR(HRT) 3.7, 95% CI 1.4 to 9.4; P<0.01).
- On the other hand, in women with the factor V Leiden mutation, the estimated risk associated with HRT was increased nearly 6-fold, although the CIs were wide and included unity (OR(HRT) 5.7, 95% CI 0.6 to 53.9; P=0.13).
- The OR for women with the Leiden mutation who were also assigned to HRT compared with wild-type women assigned to placebo was 14.1 (95% CI 2.7 to 72.4, P=0.0015).
- In women with the factor V Leiden mutation who were treated with HRT, the estimated absolute incidence of VTE was 15.4 of 1000 per year compared with 2.0 of 1000 per year in women without the mutation who were taking a placebo (P=0.0015).
- On the basis of these data, in women with coronary disease, the estimated number needed to screen for factor V Leiden to avoid an HRT-associated VTE during 5 years of treatment is 376. If factor V Leiden genotyping becomes less expensive, it could be cost effective to screen for the presence of the mutation before instituting HRT in women with coronary disease
- Factor V Leiden, hormone replacement therapy, and risk of venous thromboembolic events in women with coronary disease. Arterioscler Thromb Vasc Biol. 2002 Jun 1;22(6):1012-7.

6

But…

Department of Internal Medicine, Sections on Cardiology, Wake Forest University School of Medicine, Winston-Salem, NC 27157-1040, USA. dherring@wfubmc.edu

- In HERS, participants were randomly assigned to receive **oral** conjugated equine estrogen (0.625 mg daily) plus **medroxyprogesterone acetate** (2.5 mg daily) or placebo and were followed for an average of 4.1 years.
- In ERA, women were randomized to receive **oral** conjugated equine estrogen (0.625 mg daily), estrogen plus **medroxyprogesterone acetate** (2.5 mg daily), or placebo and were followed for 3.25 years.
- Factor V Leiden, hormone replacement therapy, and risk of venous thromboembolic events in women with coronary disease. Arterioscler Thromb Vasc Biol. 2002 Jun 1;22(6):1012-7. doi: 10.1161/01.atv.0000018301.91721.94. PMID: 12067913.

7

Concern About clots

- **Oral contraceptive use in women with factor V Leiden is associated with increased rates of venous thromboembolic events (VTEs).**
- **However, the effects of hormone replacement therapy (HRT) in postmenopausal women with factor V Leiden are not known.**
- **A nested case-control study was conducted among women with established coronary disease enrolled in 2 randomized clinical trials of HRT, the Heart and Estrogen/Progestin Replacement Study (HERS) and the Estrogen Replacement and Atherosclerosis (ERA) trial.**
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8

But… it's the route or the progestin

- Oral vs. Transdermal
- Progesterone vs. Progestin

9

Question of HRT & Coagulation disorders Study #1

- Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial.
- **Arterioscler Thromb Vasc Biol. 1997 Nov;17(11):3071-8. doi: 10.1161/01.atv.17.11.3071. PMID: 9409295**
- **Affiliation**
- [1] INSERM-Cardiovascular Epidemiology Unit U258, Hôpital Broussais, Paris, France. epicv@hbroussais.fr

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Transdermal vs oral

- Forty-five healthy postmenopausal women, aged 45 to 64 years, were assigned randomly to one of the three following groups: cyclic oral or transdermal estradiol, both combined with progesterone, or no hormonal treatment.
- Hemostatic variables were assayed at baseline and after a 6-month period.
- . Oral but not transdermal estradiol regimen significantly increased the mean value of prothrombin activation peptide (F1 + 2) and decreased mean antithrombin activity compared with no treatment.
- The oral estrogen group was associated with a significant decrease in both mean tissue-type plasminogen (t-PA) concentration and plasminogen activator inhibitor (PAI-1) activity and a significant rise in global fibrinolytic capacity (GFC) compared with the two other groups.
- A transdermal estrogen regimen had no significant effect on PAI-1, t-PA, and GFC levels.
- There were no significant changes in mean values of fibrinogen, factor VII, von Willebrand factor, protein C, fibrin D-dimer, and plasminogen between and within the three groups.
- We conclude that oral estrogen/progesterone replacement therapy may result in coagulation activation and increased fibrinolytic potential, whereas **opposed transdermal estrogen appears without any substantial effects on hemostasis**.
- **Whereas these results may account for an increased risk of venous thromboembolism in users of oral postmenopausal estrogen**, **they emphasize the potential importance of the route of estrogen administration in prescribing hormone replacement therapy to postmenopausal women**, **especially to those at high risk of thrombotic disease**.
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11

Study # 2
Inserm Unit 780, Cardiovascular Epidemiology Section, 16 Avenue Paul Vaillant Couturier, 94807 Villejuif Cedex, France.

- **Background:** Oral estrogen therapy increases the risk of venous thromboembolism (VTE) in postmenopausal women. Transdermal estrogen may be safer.
- **Methods and results:** We performed a multicenter case-control study of VTE among postmenopausal women 45 to 70 years of age between 1999 and 2005 in France.
- We recruited 271 consecutive cases with a first documented episode of idiopathic VTE (208 hospital cases, 63 outpatient cases) and 610 controls (426 hospital controls, 184 community controls) matched for center, age, and admission date.
- There was no significant association of VTE with micronized progesterone and pregnane derivatives (OR, 0.7; 95% CI, 0.3 to 1.9 and OR, 0.9; 95% CI, 0.4 to 2.3, respectively).
- In contrast, norpregnane derivatives were associated with a 4-fold-increased VTE risk (OR, 3.9; 95% CI, 1.5 to 10.0).
- The norpregnane derivatives include **nomogestrol acetate, demegestone, promegestone, trimegestone, and nesterone**. All lack a methyl group at carbon 10.
- **Conclusions:** Oral but **not transdermal estrogen** is associated with an increased VTE risk.
- In addition, our data suggest that norpregnane derivatives may be thrombogenic, whereas micronized progesterone and pregnane derivatives appear safe with respect to thrombotic risk.
- Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007 Feb 20;115(7):840-5. doi: 10.1161/CIRCULATIONAHA.106.642280. PMID: 17309934.

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Study #3 ESTHER study 2006

- **Background:** Oral estrogen use and elevated body mass index (BMI) increase the risk of venous thromboembolism (VTE). Recent data suggest that transdermal estrogen might be safe with respect to thrombotic risk. However, the impact of transdermal estrogen on the association between overweight (25 kg m(-2) < BMI < or = 30 kg m(-2)) or obesity (BMI >30 kg m(-2)) and VTE risk has not been investigated.
- **Methods:** We carried a multicenter case-control study of VTE among postmenopausal women aged 45-70 years, between 1999 and 2005, in France. Case population consisted of women with a first documented idiopathic VTE. We recruited 191 hospital cases matched with 416 hospital controls and 62 outpatient cases matched with 181 community controls.
- **Results:** The odds ratio (OR) for VTE was 2.5 [95% confidence interval (CI):1.7-3.7] for overweight and 3.9 (95% CI: 2.2-6.9) for obesity. Oral, not transdermal, estrogen was associated with an increased VTE risk (OR = 4.5; 95% CI: 2.6-7.7 and OR = 1.1; 95% CI: 0.7-1.7, respectively). Compared with non-users with normal weight, the combination of oral estrogen use and overweight or obesity further enhanced VTE risk (OR = 10.2; 95% CI: 3.5-30.2 and OR = 20.6; 95% CI: 4.8-88.1, respectively). However, transdermal users with increased BMI had similar risk as non-users with increased BMI (OR = 2.9; 95% CI: 1.5-5.8 and OR = 2.7; 95% CI: 1.7-4.5 respectively for overweight; OR = 5.4; 95% CI: 2.1-14.1 and OR = 4.0; 95% CI: 2.1-7.8 respectively for obesity).
- Conclusions: **In contrast to oral estrogen, transdermal estrogen does not confer an additional risk of idiopathic VTE in women with increased BMI**.
- EStrogen and THromboEmbolism Risk (ESTHER) Study Group. Obesity and risk of venous thromboembolism among postmenopausal women: differential impact of hormone therapy by route of estrogen administration. The ESTHER Study. J Thromb Haemost. 2006 Jun;4(6):1259-65.

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ESTHER STUDY 2007

The Estrogen and Thromboembolism Risk (ESTHER) study, adds important, relevant data to bolster the case that HT type and route of delivery do indeed make a difference.

This well-designed, French, multicenter case-control study of VTE enrolled 271 consecutive cases of VTE in women (age, 45 to 70 years) and matched them to hospital and community controls.

Current HT use was present in 46% of the VTE cases compared with 37% of controls.

Oral HT users had 4-fold-increased odds of VTE;

There was no increased risk among transdermal hormone users (odds ratio, 0.9)

Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007 Feb 20;115(7):840-5

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ESTHER Study 2008

- A total of 271 cases and 610 controls were includedinthe ESTHERstudy.
- Most current users of estrogen therapy received 17β-estradiol (except for two cases who used conjugatedequine estrogens).
- Mean dose of oral estrogen was1.5 mg per day ranging from 0.5to2mg, and the most common dailydose of transdermal estrogen was 50μg or less.
- Our results showthat **non-O blood type is a VTE risk factor** among postmenopausal women.
- These data are consistent with those from several other studies regarding the increased VTE risk among non-O blood type compared with O blood type.
- EStrogen and THromboEmbolism Risk (ESTHER) Study Group. Synergism between non-O blood group and oral estrogen in the risk of venous thromboembolism among postmenopausal women: The ESTHER study. Thromb Haemost. 2008 Jan;99(1):246-8.

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Progesterone Type

In ESTHER, type of progestogen also appeared to influence risk of VTE.

Neither micronized progesterone nor pregnane derivatives (including medroxyprogesterone acetate) were associated with VTE, whereas norpregnane derivatives were associated with a 4-fold increase in odds of VTE.

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Route of Administration type

- The data from ESTHER lend additional support to the evidence that **route of estrogen administration matters.**
- **Transdermal preparations avoid the induction of hepatic protein synthesis associated with the first-pass effect of oral estrogens**.
- **Hypercoagulant effects (higher prothrombin fragment 1+2 and factor VII levels) and increased synthesis of C-reactive protein are observed after oral but not transdermal estrogen**.
- **Transdermal estradiol also avoids peaks and nadirs in circulating concentrations**.

- Effects of oral and transdermal estrogen replacement therapy on markers of coagulation, fibrinolysis, inflammation and serum lipids and lipoproteins in postmenopausal women. **Thromb Haemost**. 2001; *85*: 619–625

17

Study #4 Department of Medicine, University of Helsinki, Finland.

- We compared the effects of oral estradiol (2 mg), transdermal estradiol (50 microg), and placebo on measures of coagulation, fibrinolysis, inflammation and serum lipids and lipoproteins in **27 postmenopausal women at baseline and after 2 and 12 weeks of treatment.**
- **Oral and transdermal estradiol induced similar increases in serum free estradiol concentrations.**
- Oral therapy increased the plasma concentrations of factor VII antigen (FVIIag) and activated factor VII (FVIIa), and the plasma concentration of the prothrombin activation marker prothrombin fragment 1+2 (F1+2).
- Oral but **not** transdermal estradiol therapy significantly lowered plasma plasminogen activator inhibitor-1 (PAI-1) antigen and tissue-type plasminogen activator (tPA) antigen concentrations and PAI-1 activity, and increased D-dimer concentrations, suggesting increased fibrinolysis.
- **The concentration of soluble E-selectin decreased and serum C-reactive protein (CRP) increased significantly in the oral but not in the transdermal or placebo groups**.
- In summary, oral estradiol increased markers of fibrinolytic activity, decreased serum soluble E-selectin levels and induced potentially antiatherogenic changes in lipids and lipoproteins.
- **In contrast to these beneficial effects, oral estradiol changed markers of coagulation towards hypercoagulability, and increased serum CRP concentrations**.
- **Transdermal estradiol or placebo had no effects on any of these parameters**.
- These data demonstrate that oral estradiol does not have uniformly beneficial effects on cardiovascular risk markers and that the oral route of estradiol administration rather than the circulating free estradiol concentration is critical for any changes to be observed.

- Effects of oral and transdermal estrogen replacement therapy on markers of coagulation, fibrinolysis, inflammation and serum lipids and lipoproteins in postmenopausal women. Thromb Haemost. 2001 Apr;85(4):619-25. PMID: 11341495.

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Study #5

Division of Obstetrics and Gynaecology, Department of Molecular and Clinical Medicine, Faculty of Health Sciences, Linkoping University, S-58185 Linkoping, Sweden

- **Objective:** To demonstrate the effects of 2-year transdermal continuous combined low-dose estradiol (0.025 mg/day) and norethisterone acetate (0.125 mg/day) on lipid/lipoprotein profile and coagulation/fibrinolysis.
- **Methods:** A double-blind, randomized, multicenter, parallel, 1-year trial enrolled **266 healthy women at least 2 years post menopause**.
- Patients received either 0.025 mg estradiol and 0.125 mg norethisterone acetate daily or placebo transdermally. One hundred and thirty five women completed a second year open follow-up (96 had used Estragest TTS, 39 placebo during the first year), where all women had the estradiol/norethisterone patch. Lipid/lipoprotein profile and coagulation/fibrinolysis parameters were studied at 0, 24, 48, 72 and 96 weeks.
- **Results:** In women on estradiol/norethisterone total cholesterol, Lp(a) and VLDL cholesterol decreased significantly more than in the placebo group after 24 weeks and LDL cholesterol after 48 weeks. Women on estradiol/norethisterone had no change in HDL, triglycerides or Lp(a), an increased HDL/total cholesterol ratio and decreased LDL, VLDL and total cholesterol at 48 weeks compared to placebo.
- Women with active treatment also showed a significant reduction compared with the placebo group of Factor VII and antithrombin III at 24 and 48 weeks and a reduction of fibrinogen at 24 weeks. These changes persisted over the second year.
- **Conclusions:** A continuous combined low-dose transdermal patch daily delivering 0.025 mg estradiol and 0.125 mg norethisterone acetate provided beneficial effects on lipid/lipoprotein profile and coagulation/fibrinolysis.
- Lipids and clotting factors during low dose transdermal estradiol/norethisterone use. Maturitas. 2005 Apr 11;50(4):344-52. doi: 10.1016/j.maturitas.2004.10.001. PMID: 15780536.

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Study #6 Study 3-Year Texas Study

- The objective of this study was to examine the long-term effects of compounded bioidentical transdermal sex steroid therapy including estriol, estradiol, progesterone, DHEA, and testosterone on cardiovascular biomarkers, hemostatic, inflammatory, immune signaling factors; quality-of-life measures; and health outcomes in peri/postmenopausal women within the context of a hormone restoration model of care.
- A prospective, cohort, closed-label study received approval from the Human Subjects Committee. Recruitment from outpatient clinics at an academic medical center and the community at large resulted in **three hundred women giving signed consent**.
- Stephenson K, Neuenschwander PF, Kurdowska AK. The effects of compounded bioidentical transdermal hormone therapy on hemostatic, inflammatory, immune factors; cardiovascular biomarkers; quality-of-life measures; and health outcomes in perimenopausal and postmenopausal women. Int J Pharm Compd. 2013 Jan-Feb;17(1):74-85. PMID: 23627249.

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75 women on BHRT for 36 months

- Seventy-five women who met strict inclusion/exclusion criteria were enrolled. Baseline hormone evaluation was performed along with baseline experimental measures. Following this, women received compounded transdermal bioidentical hormone therapy of BiEst (80%Estriol/20%Estradiol), and/or Progesterone for eight weeks to meet established physiologic reference ranges for the luteal phase in premenopausal women.
- The luteal phase hormone ratios were selected based on animal and epidemiologic studies demonstrating favorable outcomes related to traumatic, ischemic, or neuronal injury.
- Follow-up testing was performed at eight weeks and adjustment to hormone regimens were made including addition of androgens of DHEA and Testosterone if indicated.
- Experimental subjects were monitored for 36 months. Baseline, 2-month, and annual values were obtained for: blood pressure, body mass index, fasting glucose, Homeostasis Metabolic Assessment of Insulin Resistance (HOMA-IR), fasting triglycerides, total Factor VII, Factor VIII, fibrinogen, Antithrombin III, Plasminogen Activator Inhibitor1(PAL-1), C-reactive protein (CRP), Interleukin-6 (IL-6), Matrix Metalloproteinase-9 (MMP-9), Tumor Necrosis Factor-alpha (TNF), Insulin-like Growth Factor (IGF-1), and sex steroid levels.

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3-Year Texas Study

- Psychosocial measures included: Greene Climacteric Scale, Visual Analog Pain Scale, Hamilton Anxiety Scale, Hamilton Depression Scale, Holmes Rahe Stress Scale, Job Strain, and Home Strain.
- Health outcome measures included the number of prescribed medications used, number of co-morbidities, and endometrial thickness in postmenopausal women with intact uteri.
- Subjects receiving **compounded transdermal bioidentical hormone therapy** showed **significant favorable** changes in: Greene Climacteric Scale scores, Hamilton Anxiety Scale, Hamilton Depression Scale, Visual Analog Pain Scale, fasting glucose, fasting triglycerides, **MMP-9, C-reactive Protein, fibrinogen, Factor VII, Factor VIII, Insulin-Like Growth Factor 1**, and health outcomes of co-morbidities and a number of prescribed medications.
- Antithrombin III levels were significantly decreased at 36 months. Antithrombin is a natural anticoagulant that inhibits the activated coagulation factors thrombin (factor IIa), factor Xa, and, to a lesser extent, factor XIa and factor IXa.
- **One issue is a genetic insufficient level of antithrombin III.**
- Administration of compounded transdermal bioidentical hormone therapy in doses targeted to physiologic reference ranges administered in a daily dose significantly relieved menopausal symptoms in peri/postmenopausal women.
- **Cardiovascular biomarkers, inflammatory factors, immune signaling factors, and health outcomes were favorably impacted, despite very high life stress, and home and work strain in study subjects.**
- **The therapy did not adversely alter the net prothrombotic potential, and there were no associated adverse events.**

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Editorial #8
Are Some Types of Hormone Therapy Safer Than Others?
Lessons From the Estrogen and Thromboembolism Risk Study Circulation Vol 115 #7 Fe 2007

Results of clinical trials[4,5] and observational studies[6] have been concordant in demonstrating an increased risk of VTE with oral exogenous HT.

Recent studies suggest that VTE risk may be lower with transdermal than oral estrogen and with estrogen alone than with combined therapy.

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Study #7

Department of Medicine, McMaster University and St. Joseph's Hospital, Hamilton, Ontario, Canada.
jdouket@mcmaster.ca

- **Recent findings:** The risk for venous thromboembolism seems to be less in users of estrogen-only hormone replacement therapy (odds ratio = 1.2; 95% confidence interval: 0.6-2.6) than in users of estrogen-progestin hormone replacement therapy (odds ratio = 2.7; 95% confidence interval: 1.4-5.1),
- **And there may be no increased risk for venous thromboembolism with transdermal hormone replacement therapy** (odds ratio = 1.0; 95% confidence interval: 0.3-3.3).
- The presence of a prothrombotic blood abnormality, such as the factor V Leiden mutation, seems to further increase the risk for venous thromboembolism in hormone replacement therapy users (odds ratio = 17.1; 95% confidence interval: 3.7-78).
- Continued use of hormone replacement therapy in the perioperative period does not seem to have an impact on the overall risk for postoperative venous thromboembolism (odds ratio = 0.66; 95% confidence interval: 0.35-1.18).
- Hormone replacement therapy and risk for venous thromboembolism: what's new and how do these findings influence clinical practice? Curr Opin Hematol. 2005 Sep;12(5):395-400. doi: 10.1097/01.moh.0000161047.53353.a8. PMID: 16093786.

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Study #8

- **Methods:** Eighty-eight women were randomized to four groups receiving continuous transdermal estradiol 50 microg/day (tE2), oral conjugated equine estrogen 0.625 mg/day (CEE 0.625 mg), oral conjugated equine estrogen 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day (CEE 0.625 mg/MPA 2.5 mg), or oral 2 mg 17-beta estradiol combined with 1 mg norethistrone acetate (E2/norethistrone). The hysterectomized patients received only estrogen, and the remaining women received the estrogen plus progesterone combination regimens. As a marker of hemostatic system fibrinogen, tissue plasminogen activator (tPA), and plasminogen activator inhibitor-1 (PAI-1) levels were measured initially, and after 1 and 6 months of therapy.
- **Results:** The treatment groups were well matched for baseline characteristics including age, height, weight, body mass index, and systolic and diastolic blood pressures. During the study period fibrinogen levels were below the baseline values in all groups. However, the decrease was only statistically significant in patients treated with oral 0.625 mg/day CEE. tPA levels were decreased significantly by tE2, CEE 0.625 mg, and CEE 0.625 mg/MPA 2.5 mg. PAI-1 levels were decreased significantly by CEE 0.625 mg, and CEE 0.625 mg/MPA 2.5 mg. When the effects of the four different regimens were compared using percentage changes from the baseline, no significant difference was found among the treatment groups.
- **Conclusion:** One of the treatment regimens resulted in a more coagulable state. Oral therapy with CEE decreased the levels of all parameters, and MPA did not impair this beneficial effect, except for in fibrinogen. Transdermal therapy had a minimal effect. No significant difference was noted among the four regimens.
- Effects of four different regimens of hormone replacement therapy on hemostatic parameters: a prospective randomized study. Maturitas. 2006 Feb 20;53(3):267-73. doi: 10.1016/j.maturitas.2005.05.010. Epub 2005 Jun 22. PMID: 15978753.

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OCP Hypertension

- **Background:** Oral contraceptives induce hypertension in approximately 5% of users of high-dose pills that contain at least 50 micrograms estrogen and 1 to 4 mg progestin, and small increases in blood pressure have been reported even among users of modern low-dose formulations. However, neither the responsible hormone in the oral contraceptive nor particular subgroups of women who might be susceptible to the hypertensive effect of oral contraceptives have been identified.
- **Methods and results:** In a prospective cohort study in the United States, 68 297 female nurses aged 25 to 42 years and free of diagnosed hypertension, diabetes, coronary heart disease, stroke, and cancer at baseline were followed up for 4 years. During 231 006 person-years of follow-up, 1567 incident cases of hypertension were diagnosed. Compared with women who had never used oral contraceptives, the age-adjusted relative risk was 1.5 (95% CI = 1.2 to 1.8) for current use and 1.1 (95% CI = 0.9 to 1.2) for past use. After adjustment for age, body mass index, hormones cigarette smoking, family history of hypertension, parity, physical activity, alcohol intake, and ethnicity, current users of oral contraceptives had an increased risk of development of hypertension (RR = 1.8; 95% CI = 1.5 to 2.3) compared with women who had never used them. The multivariate relative risk for past users was 1.2 (95% CI = 1.0 to 1.4). There were no important modifying effects of age, family history of hypertension, ethnicity, or body mass index.
- **Conclusions:** Current users of oral contraceptives had a significant, moderately increased risk of hypertension. However, among this group, only 41.5 cases per 10 000 person-years could be attributed to oral contraceptive use. Risk decreased quickly with cessation of oral contraceptives, and past users appeared to have only a slightly increased risk.

- Circulation 1996 Aug 1;94(3):483-9.
- doi: 10.1161/01.cir.94.3.483. Prospective study of oral contraceptives and hypertension among women in the United States

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Study #8

Department of Gynecology and Obstetrics, University Hospital of Maribor, Maribor, Slovenia

- **Objective: Androgenic progestins such as norethisterone acetate (NETA) may influence the effect of estradiol (E_2) therapy**.
- We compared the influence of oral E(2), with and without NETA, and transdermal E(2) on markers of coagulation, fibrinolysis, and inflammation and on lipids and lipoproteins in healthy postmenopausal women.
- **Design:** A total of 112 healthy postmenopausal women were randomized to receive treatment with either oral E(2), with or without NETA, transdermal E(2), or placebo. At baseline and after 28 weeks, levels of serum lipids and lipoproteins and markers of coagulation, fibrinolysis, and inflammation were determined.
- **Conclusions:** Oral E(2), with or without NETA, produced no net activation of coagulation but improved fibrinolysis.
- **Both modes of oral menopausal hormone therapy have a greater impact on markers of inflammation, coagulation, fibrinolysis, lipids, and lipoproteins than transdermal E_2.**
- The effect of various menopausal hormone therapies on markers of inflammation, coagulation, fibrinolysis, lipids, and lipoproteins in healthy postmenopausal women. Menopause. 2006 Jul-Aug;13(4):643-50. doi: 10.1097/01.gme.0000198485.70703.7a. PMID: 16837886.

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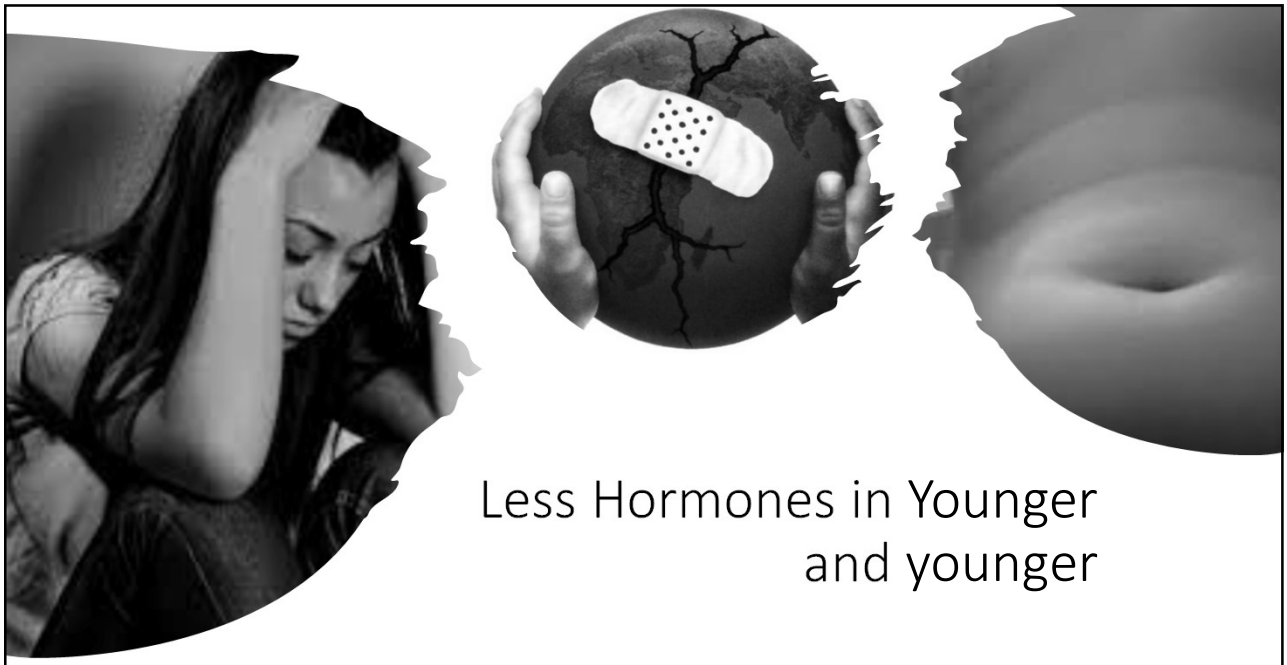

Less Hormones in Younger and younger

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Low T Israeli epidemic

- Background: Several studies from the US and Europe have shown a population-level decline in serum testosterone in men from 1970's to early 2000's.
- However, to the best of our knowledge, no study examining population-level decline in testosterone has been published in more recent years.
- The study objective was therefore to examine secular trends in testosterone levels among Israeli men in the first and second decades of the twenty-first century,
- Secular trends in testosterone- findings from a large state-mandate care provider. Reprod Biol Endocrinol. 2020 Mar 9;18(1):19. doi: 10.1186/s12958-020-00575-

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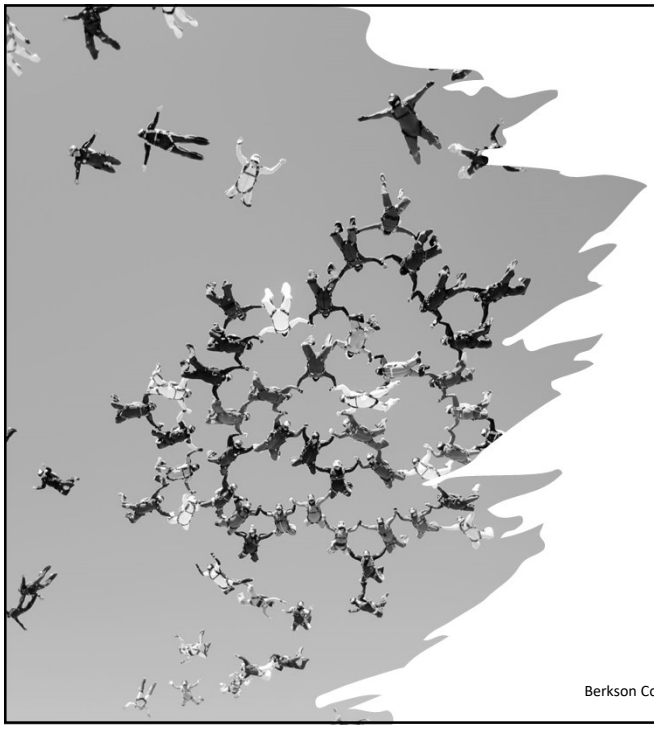

Low T

- Testosterone levels in American men have been declining steadily over the past two decades.
- ***CONCLUSIONS:***
- Both chronological aging and changes in health and lifestyle factors are associated with declines in serum T.
- Comorbidities and lifestyle influences may be as strongly associated with declining T levels as is aging itself over the short- to midterm.
- These results suggest the possibility that age-related hormone decline may be decelerated through the management of health and lifestyle factors.
- J Clin Endocrinol Metab. 2007 Feb;92(2):549-55. **The relative contributions of aging, health, and lifestyle factors to serum testosterone decline in men.**

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Israel

All incident total testosterone performed between1/2006 and 3/2019 among 102,334 male members of a large health organization.

A significant ($p < 0.001$) and prominent trend of age-independent decline in the testosterone levels was recorded during the study period for most age groups.

There was a highly significant age-independent decline in total testosterone in the first and second decades of the twenty-first century.

The decline was unlikely to be explained by increasing rates of obesity.

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USA New England research institute

Design: We describe a prospective cohort study of health and endocrine functioning in randomly selected men of age 45-79 yr. We provide three data collection waves: baseline (T1: 1987-1999) and two follow-ups (T2: 1995-1997, T3: 2002-2004).

Setting: This was an observational study of randomly selected men residing in greater Boston, Massachusetts.

Participants: Data obtained from 1374, 906, and 489 men at T1, T2, and T3, respectively, totaling 2769 observations taken on 1532 men.

Main outcome measures: The main outcome measures were serum total T and calculated bioavailable T.

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NEW England Study Low T

Results: We observe a substantial age-independent decline in T that does not appear to be attributable to observed changes in explanatory factors, including health and lifestyle characteristics such as smoking and obesity.

The estimated population-level declines are greater in magnitude than the cross-sectional declines in T typically associated with age.

Conclusions: These results indicate that recent years have seen a substantial, and as yet unrecognized, age-independent population-level decrease in T in American men, potentially attributable to birth cohort differences or to health or environmental effects not captured in observed data.

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Low Serum Testosterone and Mortality in Male Veterans

- **Background:** Low serum testosterone is a common condition in aging associated with decreased muscle mass and insulin resistance.
- This study evaluated whether low testosterone levels are a risk factor for mortality in male veterans.
- **Methods:** We used a clinical database to identify men older than 40 years with repeated testosterone levels obtained from October 1, 1994, to December 31, 1999, and without diagnosed prostate cancer. A low testosterone level was a total testosterone level of less than 250 ng/dL (<8.7 nmol/L) or a free testosterone level of less than 0.75 ng/dL (<0.03 nmol/L). Men were classified as having a low testosterone level (166 [19.3%]), an equivocal testosterone level (equal number of low and normal levels) (240 [28.0%]), or a normal testosterone level (452 [52.7%]). The risk for all-cause mortality was estimated using Cox proportional hazards regression models, adjusting for demographic and clinical covariates over a follow-up of up to 8 years.
- **Results:** Mortality in men with normal testosterone levels was 20.1% (95% confidence interval [CI], 16.2%-24.1%) vs 24.6% (95% CI, 19.2%-30.0%) in men with equivocal testosterone levels and 34.9% (95% CI, 28.5%-41.4%) in men with low testosterone levels. After adjusting for age, medical morbidity, and other clinical covariates, low testosterone levels continued to be associated with increased mortality (hazard ratio, 1.88; 95% CI, 1.34-2.63; P<.001) while equivocal testosterone levels were not significantly different from normal testosterone levels (hazard ratio, 1.38; 95% CI, 0.99%-1.92%; P=.06). In a sensitivity analysis, men who died within the first year (50 [5.8%]) were excluded to minimize the effect of acute illness, and low testosterone levels continued to be associated with elevated mortality.
- **Conclusions**: **Low testosterone levels were associated with increased mortality in male veterans**
- Low serum testosterone and mortality in male veterans. Arch Intern Med. 2006 Aug 14-28;166(15):1660-5. doi: 10.1001/archinte.166.15.1660. PMID: 16908801.

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What about T?
↓T ↑Premature Mortality

- We explored the relationship between testosterone levels and premature death in a large US population.
- We found that low testosterone is associated with both premature death and related disease processes such as obesity,
- Both of which can be initially treated with diet and exercise.
- But then need TR.

- [a]Department of Urology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
- [b]Department of Surgery, NorthShore University Health System, Chicago, IL, USA
- [c]Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins, Baltimore, MD, USA

- Serum Total Testosterone and Premature Mortality Among Men in the USA. Eur Urol Open Sci. 2021 Jun 7;29:89-92. doi: 10.1016/j.euros.2021.05.008. PMID: 34337538; PMCID: PMC8317905.

 36

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Endogenous Testosterone and Mortality Due to All Causes, Cardiovascular Disease, and Cancer in Men

- European Prospective Investigation Into Cancer in Norfolk (EPIC-Norfolk) Prospective Population Study
- ***Background—*** The relation between endogenous testosterone concentrations and health in men is controversial.
- ***Methods and Results—*** We examined the prospective relationship between endogenous testosterone concentrations and mortality due to all causes, cardiovascular disease, and cancer in a nested case-control study based on 11 606 men aged 40 to 79 years surveyed in 1993 to 1997 and followed up to 2003. Among those without prevalent cancer or cardiovascular disease, 825 men who subsequently died were compared with a control group of 1489 men still alive, matched for age and date of baseline visit. Endogenous testosterone concentrations at baseline were inversely related to mortality due to all causes (825 deaths), cardiovascular disease (369 deaths), and cancer (304 deaths). Odds ratios (95% confidence intervals) for mortality for increasing quartiles of endogenous testosterone compared with the lowest quartile were 0.75 (0.55 to 1.00), 0.62 (0.45 to 0.84), and 0.59 (0.42 to 0.85), respectively (P<0.001 for trend after adjustment for age, date of visit, body mass index, systolic blood pressure, blood cholesterol, cigarette smoking, diabetes mellitus, alcohol intake, physical activity, social class, education, dehydroepiandrosterone sulfate, androstanediol glucuronide, and sex hormone binding globulin). An increase of 6 nmol/L serum testosterone (≈1 SD) was associated with a 0.81 (95% confidence interval 0.71 to 0.92, P<0.01) multivariable-adjusted odds ratio for mortality. Inverse relationships were also observed for deaths due to cardiovascular causes and cancer and after the exclusion of deaths that occurred in the first 2 years.
- ***Conclusions—*** In men, endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes. Low testosterone may be a predictive marker for those at high risk of cardiovascular disease.
- **Endogenous Testosterone and Mortality Due to All Causes, Cardiovascular Disease, and Cancer in Men** 26 Nov 2007https://doi.org/10.1161/CIRCULATIONAHA.107.719005Circulation. 2007;116:2694–2701

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Young Males

- **Abstract**
- Hypogonadism and its therapies have a significant impact on male fertility potential. It is necessary to determine the etiology to treat and counsel the patient appropriately on therapeutic options.
- For the hypogonadal male on exogenous testosterone, management should begin with cessation of the exogenous testosterone and supplemental subcutaneous human chorionic gonadotropin and an oral follicle-stimulating hormone (FSH)-inducing agent to allow reestablishment of the hypothalamic-pituitary-gonadal axis and spermatogenesis. Further supplemental therapy with recombinant FSH in some patients may be necessary to achieve optimal semen parameters.
- Division of Male Reproductive Medicine and Surgery, Scott Department of Urology, Baylor College of Medicine, Houston, TX 77030, USA.
- [2]Division of Male Reproductive Medicine and Surgery, Scott Department of Urology, Baylor College of Medicine, Houston, TX 77030, USA. Electronic address: larryl@bcm.edu
- Testosterone and Male Infertility. Urol Clin North Am. 2016 May;43(2):195-202. doi: 10.1016/j.ucl.2016.01.006. Epub 2016 Mar 19. PMID: 27132576.

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Injection of testosterone may be safer and more effective than transdermal administration for combating loss of muscle and bone in older men

- The value of testosterone replacement therapy (TRT) for older men is currently a topic of intense debate.
- While US testosterone prescriptions have tripled in the past decade (9), debate continues over the risks and benefits of TRT.
- TRT is currently prescribed for older men with either low serum testosterone (T) or low T plus accompanying symptoms of hypogonadism.
- The normal range for serum testosterone is 300 to 1,000 ng/dl.
- Serum T ≤ 300 ng/dl is considered to be low, and T ≤ 250 is considered to be frank hypogonadism.
- Most experts support TRT for older men with frank hypogonadism and symptoms.
- Treatment for men who simply have low T remains somewhat controversial

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Route of Delivery For Males Matters

- TRT is most frequently administered by intramuscular (im) injection of long-acting T esters or transdermally via patch or gel preparations and infrequently via oral administration.
- TRT produces a number of established benefits in hypogonadal men, including increased muscle mass and strength, decreased fat mass, increased bone mineral density, and improved sexual function, and in some cases those benefits are dose dependent.
- For example, doses of TRT administered by im injection are typically higher than those administered transdermally, which results in greater musculoskeletal benefits.
- TRT also produces known risks including development of polycythemia (Hct > 50) in 6% of those treated, decrease in HDL, breast tenderness and enlargement, prostate enlargement, increases in serum PSA, and prostate-related events and may cause suppression of the hypothalamic-pituitary-gonadal axis.
- **Importantly, TRT does not increase the risk of prostate cancer**. Putative risks include edema and worsening of sleep apnea. Several recent reports have also indicated that TRT may produce cardiovascular (CV) risks, while others report no risk or even benefit.
- To address the potential CV risks of TRT, we have recently reported via meta-analysis that oral TRT increases CV risk and suggested that the CV risk profile for im TRT may be better than that for oral or transdermal TRT.

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Affiliations

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[2]Research Service, Veterans Affairs Medical Center, Gainesville, Florida; and Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, Florida.

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Do Not Create infertility by Prescribing T to Males Wanting Fertility

- In past few years we observed the increasing of population of men, who are treated with testosterone due to hypogonadism associated with aging but the most of them have no indications to testosterone replacement therapy.
- The classical symptoms of hypogonadism including depression, loss of libido, erectile dysfunction, and fatigue may be related to any others diseases.
- The increase in prevalence of androgenic anabolic steroids specifically among younger athletes is also observed.
- Exogenous testosterone and anabolic androgenic steroids can inhibit the hypothalamic-pituitary-gonadal axis leading to decreasing of endogenous testosterone synthesis and impaired spermatogenesis.
- In hypogonadal men who are in reproduction age the goal of therapy should be not only replacement therapy but also achiving and/or maintaining of spermatogenesis.
- Human chorionic gonadotropin (hCG) and selective estrogens receptor modulators (SERM) are efficacy in treatment of clinical signs and symptoms of hypoigonadism, has been shown to reverse spermatogenesis disturbances and can to maintain elevated intratesticular testosterone levels necessary to optimal spermatogenesis.
- [The treatment of hypogonadism and maintenance of fertility in men]. Pol Merkur Lekarski. 2016 Mar;40(237):198-201. Polish. PMID: 27088205.

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Indications for the use of human chorionic gonadotropic hormone for the management of infertility in hypogonadal men

- Hypogonadism among men desiring fertility preservation presents a unique challenge to physicians. Over the past decade the number of younger men with hypogonadism has increased dramatically. These men are often treated with testosterone replacement therapy (TRT) which can result in azoospermia and potentially infertility. Human chorionic gonadotropin (hCG) therapy can help re-establish or maintain spermatogenesis in hypogonadal men. We review the indications, and discuss the current evidence for the role of hCG in men with hypogonadism.
- Department of Urology, University of Miami Miller School of Medicine, Miami, FL, USA
- Indications for the use of human chorionic gonadotropic hormone for the management of infertility in hypogonadal men. Transl Androl Urol. 2018 Jul;7(Suppl 3):S348-S352. doi: 10.21037/tau.2018.04.11. PMID: 30159241; PMCID: PMC6087849.

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HCG

- The importance of the therapeutic human chorionic gonadotropin (hCG) treatment has grown tremendously over the last couple decades due to an exponential increase in the prevalence of hypogonadism in younger men and the use of anabolic androgenic steroids (AAS).
- From 2001 to 2011 men on testosterone replacement therapy (TRT) increased three fold overall and 4 times more among men aged 40–49 (1).
- The overall prevalence of hypogonadism in American men is 7% in men younger than 40 years and 38% in men over the age of 45 (2,3).
- The use of AAS has been found to be as high as 3 million amongst American men (3) and have a life time of prevalence use of 3.0% to 4.2% (4).
- This increase has occurred along with steady increase in age of paternity (5) creating an evolving challenge of treating hypogonadism and preserving fertility.

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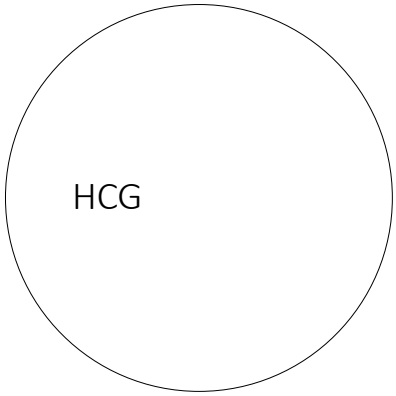

- Luteinizing hormone (LH) in the male is produced by the anterior pituitary in response to pulsatile secretion of gonadotropic releasing hormone (GnRH) from the hypothalamus.
- It acts on Leydig cells in the testicles promoting the production of testosterone.
- In men with hypogonadotropic hypogonadism (HH), or men with decreased LH secondary to exogenous testosterone use, the lack of LH results in severely decreased intratesticular testosterone levels.
- Without intratesticular testosterone spermatogenesis is impaired, and by replacing lost LH production with hCG, spermatogenesis can be restored by restoring adequate levels of intratesticular testosterone.
- hCG has also found a prominent role in treating endocrine failure of the testicle in men with anabolic steroid induced hypogonadism. These men have lost the ability to produce their own testosterone and hCG has been indicated as a part of an algorithm to help recover endogenous testosterone production (a).

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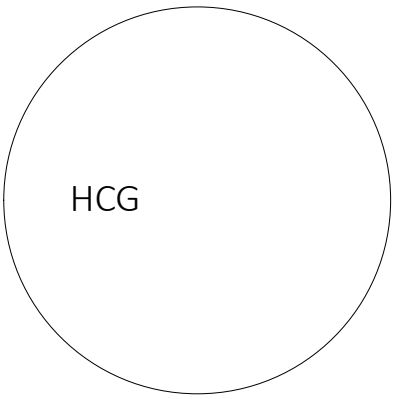

- Finally, hCG has also been used to reduce some of the side effects of TRT, mainly preventing testicular atrophy and helping maintain response to TRT by “cycling off” TRT with a periodic replacement of therapy with hCG.H

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Indications for hCG in combination with TRT

- Preserving spermatogenesis with TRT
- Exogenous steroid use impairs spermatogenesis by promoting negative feedback on both the hypothalamus and pituitary gland. This reduces the pulsatile secretion of GnRH and LH respectively. The loss of LH secretion shuts down the production of testosterone by Leydig cells which in turn significantly reduces intratesticular testosterone levels. This altering of the hypothalamus-pituitary-gonadal (HPG) axis and drop of intratesticular testosterone can lead to azoospermia within 10 weeks of starting TRT (10). Even more alarming is the fact that up to 10% of men can remain azoospermic after the cessation of TRT.
- hCG therapy can help preserve spermatogenesis in men undergoing TRT by maintaining intratesticular testosterone levels. It was has been shown that follicle stimulating hormone (FSH) alone cannot initiate or maintain spermatogenesis in hypogonadal (11) men leading to the discovery of the importance of intratesticular testosterone in spermatogenesis. In healthy eugonadal men selected to undergo TRT it was shown that their intratesticular testosterone levels dropped by 94%. However, in those who received 250 IU SC every other day along with TRT their intratesticular testosterone levels only dropped 7%. Additionally, in men who received TRT and 500 IU of hCG every other day an increase in intratesticular testosterone by 26% was observed (12). This proved that co-administering low dose hCG could maintain intratesticular testosterone in those undergoing TRT. It was later shown that not only is intratesticular testosterone increased with co-administration hCG but spermatogenesis is preserved as well at one year follow up (13). These studies proved that by concomitant hCG administration with TRT spermatogenesis and thus potentially fertility could be preserved.

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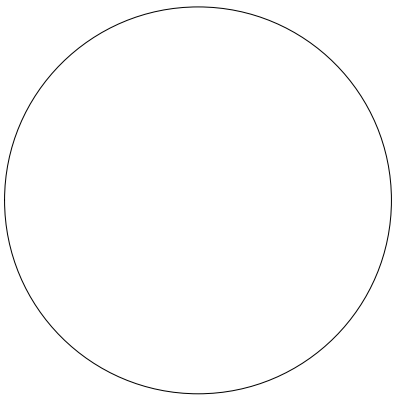
- Based off this evidence an algorithm was suggested for the simultaneous treatment of hypogonadism and preservation of fertility.
- All men wishing to preserve fertility while on TRT should have a baseline semen analysis (SA).
- Next it is important to determine the appropriate dosing regimen of hCG based off the timeline for desired pregnancy.
- For men who wish to obtain pregnancy within six months it was suggested to discontinue TRT and start 3,000 IU of hCG intramuscular, or subcutaneous every other day. SA should then be performed every two months. Clomiphene citrate 25–50 mg PO daily can be added or omitted to promote FSH production. We suggest including of clomiphene citrate in all men who are already oligospermic or azoospermic. It can be omitted in men who are initiating TRT and hCG simultaneously and have normal semen parameters.



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HCG

- If Semen parameters fail to improve and FSH remains low, Gonal-f (recombinant FSH) 75 IU every other day can be added.
- In men who desire pregnancy within 6–12 months TRT can be continued with co-administration of 500 IU of HCG every other day ± clomiphene citrate can be used.
- When planning for pregnancy in greater than 12 months TRT should be cycled off every six months replaced by a four-week cycle of 3,000 IU of hCG every other day.
- For men who do not desire to preserve fertility testicular size can me maintained while undergoing TRT with 1,500 IU of HCG given weekly.
- Which is enough to maintain pre-TRT levels of intratesticular Testosterone. *Table 1* summarizes recommendations for preserving spermatogenesis in men on TRT (16).

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Indications for the use of human chorionic gonadotropic hormone for the management of infertility in hypogonadal men. Transl Androl Urol. 2018 Jul;7(Suppl 3):S348-S35.

Department of Urology, University of Miami Miller School of Medicine, Miami, FL,

Summary of recommendations for maintenance of spermatogenesis with TRT or AAS use

Timing of desired pregnancy	Treatment recommendation
<6 months	Stop TRT/AAS
	Start 3,000 IU hCG every other day ± clomiphene citrate 25 mg oral daily
	Semen analysis every 2 months
	No FSH response: discontinue clomiphene and add rhFSH 75 IU every other day
6–12 months	Continue TRT
	Start 500 IU hCG every other day ± clomiphene citrate 25 mg oral daily
>12 months	Continue TRT
	Cycle off TRT/AAS every 6 months with a 4-week cycle of 3,000 IU hCG every other day

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B6 –hormone signal squatting time on receptor

- Optimal level of B6 – healthy signaling time
- Deficiency of B6 – excessive signaling time
- Think of estrogen sitting on a receptor like sitting on a seat
- And the time on the seat is ruled by B6 blood and local tissue levels

- World Rev Nutr Diet. 1987;51:140-88. **Oestrogens and vitamin B6--actions and interactions.**
- Br J Nutr. 1989 May;61(3):619-28. **Effects of vitamin B6 deficiency and repletion on the uptake of steroid hormones into uterus slices and isolated liver cells of rats.**
- J Biol Chem. 1992 Feb 25;267(6):3819-24. **Vitamin B6 modulates transcriptional activation by multiple members of the steroid hormone receptor superfamily.**

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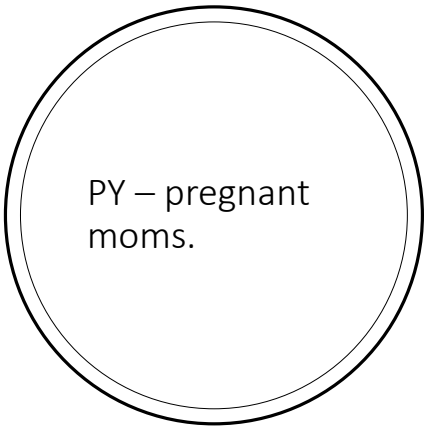

- Pyridaben (PY) is a widely used organochlorine acaricide, which can be detected **in the peripheral blood of pregnant women.**
- A substance **used** to destroy pests of the subclass Acari (mites and ticks.

- Pyridoxal 5'-phosphate alleviates prenatal pyridaben exposure-induced anxiety-like behaviors in offspring. Environ Sci Ecotechnol. 2022 Nov 14;13:100224. doi: 10.1016/j.ese.2022.100224. PMID: 36437888; PMCID: PMC9691908.

52

Call For "Green Pregnancy"

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Anxiety

- Previous research suggests that individuals with a prior history of pesticide poisoning are at increased risk of psychiatric disorder (Freire and Koifman, 2013), but findings regarding the impact of cumulative low-level exposure are inconsistent. T
- he aim of the current study was to investigate whether sheep farmers with a history of low-level exposure to organophosphate pesticides (1) report a higher level of psychological distress on subjective symptom questionnaires, compared to unexposed controls (2) also meet internationally agreed diagnostic criteria for a psychiatric disorder more often than unexposed controls.
- 127sheep farmers were evaluated and compared to 78 unexposed controls, matched in terms of gender, education, level of intelligence, working status and area of residence. Both self-report measures and structured clinical interviews were used to assess mental health.
- The exposed cohort reported significantly higher rates of anxiety and depression when self-report questionnaires were used to evaluate mood, even when stressful life events, demographic and physical health factors were taken into account. However, when diagnostic interviews were used to assess mood, this pattern only held true for anxiety.
- Anxiety and depression following cumulative low-level exposure to organophosphate pesticides. Environ Res. 2016 Nov;151:528-536. doi: 10.1016/j.envres.2016.08.020. Epub 2016 Aug 27. PMID: 27575752.

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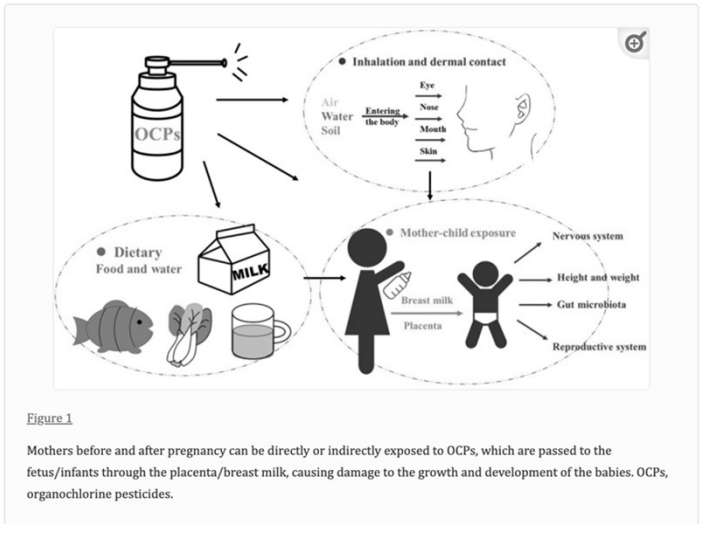

Figure 1

Mothers before and after pregnancy can be directly or indirectly exposed to OCPs, which are passed to the fetus/infants through the placenta/breast milk, causing damage to the growth and development of the babies. OCPs, organochlorine pesticides.

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Organochlorine Exposure – Veggies versus animal foods

- **Dietary exposure accounts for more than 90% of the total body burden of organochlorines**
- **OCPs tend to slowly bioaccumulate in the food chain, such that they are eventually ingested by women and enriched in adipose tissues;**
- **in these tissues, OCPs can persist for a long period of time.**
- **The highest residues of these compounds are found in fish, meat, poultry, eggs, milk and dairy products, as well as vegetable oils, nuts, avocados, sesame or olives**
- **For example, fruits and grains are the main sources of DDE .**
- **The level of DDT in breast milk is closely related to the consumption of animal-derived food and aquatic food.**
- **Of these, bioaccumulation of organic compounds in fish and other animals and their products (meat and dairy) contributes to substantial exposure to OCPs in humans through ingestion due to their high fat solubility.**
- **It has been observed that vegetarians i.e. ethose who consume vegetables, fruits and grains without animal products) have significantly lower levels of organochlorine compared to those who consume animal products.**

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Organochlorine exposure

- **However, it is not to say that vegetables do not cause the accumulation of OCPs.**
- **In one study, food preferences in vegetables were found to be correlated with HCB, HCHs (ΣHCHs, β-HCH, γ-HCH), *p,p′*-DDE and heptachlor (Σ heptachlor and trans-heptachlor epoxides) in breast milk concentrations were significantly positively correlated.**
- **In addition to contamination of dairy products through the animals themselves, a major source of dairy contamination may be the presence of OCPs such as HCH and DDT in dry and green feeds.**
- **Untreated agricultural wastewater (including pesticides, etc.) released into the water may cause the accumulation of organochlorines, leading to pollution of the aquatic ecosystem.**
- **At the same time, it also led to the pollution of aquatic organisms such as fish and shrimp.**

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Hormone Balance & protect

- Medicinal plants help cure a wide variety of diseases and form the backbone of the herbal nutraceutical industry.
- Translocation of heavy metals such as cadmium, arsenic and lead, which are known to exhibit endocrine-disrupting properties, antagonizes these plants' medicinal properties (Tripathi et al. 2021).
- The innovative fluorescent technique enabled the detection of carbamate residues in Chinese medicinal plants (Wei et al. 2018).
- Carbamate and the organophosphate group of pesticides are potent endocrine disruptors and exert action by binding to the Androgen receptor.
- Endocrine Disruptors-'Food' for Thought. Proc Zool Soc. 2021;74(4):432-442. doi: 10.1007/s12595-021-00414-1. Epub 2021 Dec 1. PMID: 34866764; PMCID: PMC8632730.

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Wherever receptors live, hormones signal

- Reproductive Tissue
- Brain
- Gut
- Eyes
- Heart
- Lining of blood vessel
- Immune cells like T-reg cells

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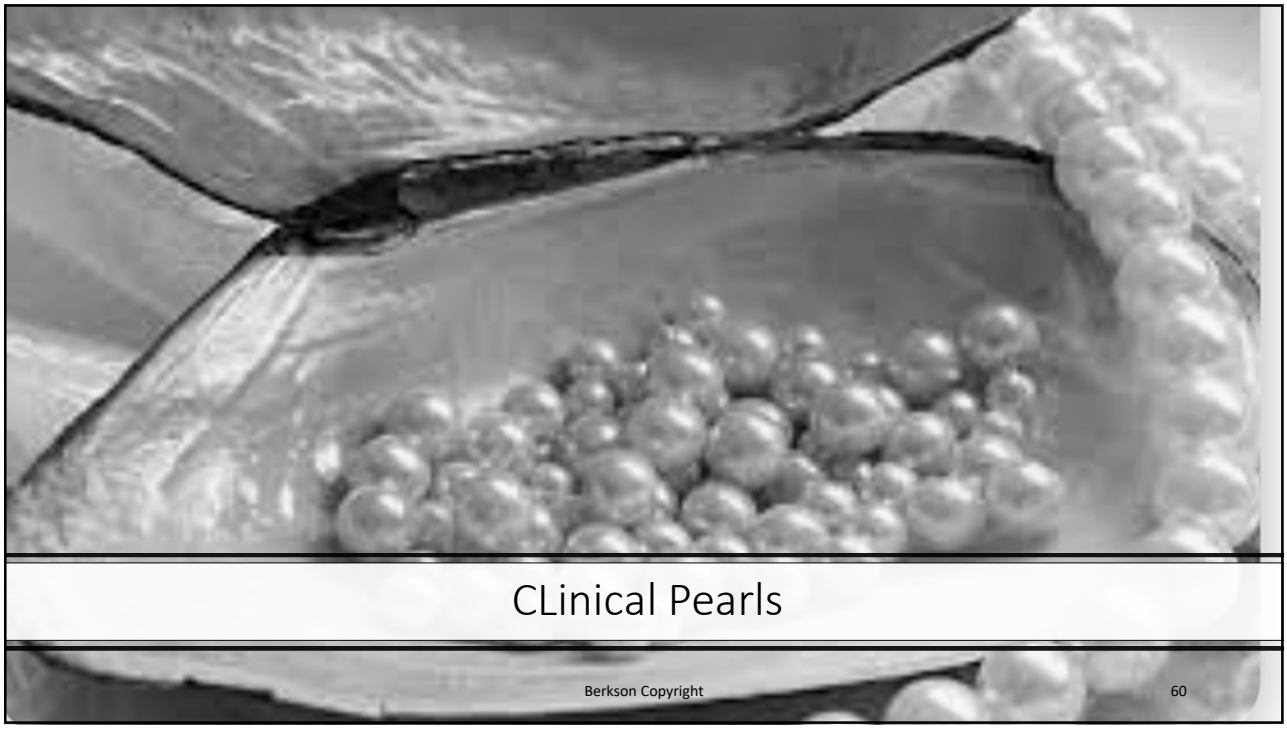

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Knowledge is power - FSH

Aging woes from too little sex steroid or too much FSH.

SEX STEROIDS

FSH

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FSH

- **Weight**
- **Bone**
- **Cognition**
- Menopause is associated with bone loss and enhanced visceral adiposity.
- A polyclonal antibody that targets the β-subunit of the pituitary hormone follicle-stimulating hormone (Fsh) increases bone mass in mice.
- Here, we report that this antibody sharply reduces adipose tissue in wild-type mice, phenocopying genetic haploinsufficiency for the Fsh receptor gene Fshr. The antibody also causes profound beiging, increases cellular mitochondrial density, activates brown adipose tissue and enhances thermogenesis. These actions result from the specific binding of the antibody to the β-subunit of Fsh to block its action. Our studies uncover opportunities for simultaneously treating obesity and osteoporosis.
- Blocking FSH induces thermogenic adipose tissue and reduces body fat. Nature. 2017 Jun 1;546(7656):107-112. doi: 10.1038/nature22342. Epub 2017 May 24. PMID: 28538730; PMCID: PMC5651981.

62

FSH - Cognition

- Alzheimer's disease has a higher incidence in older women, with a spike in cognitive decline that tracks with visceral adiposity, dysregulated energy homeostasis and bone loss during the menopausal transition.
- Inhibiting the action of follicle-stimulating hormone (FSH) reduces body fat, enhances thermogenesis, increases bone mass and lowers serum cholesterol in mice.
- Here we show that FSH acts directly on hippocampal and cortical neurons to accelerate amyloid-β and Tau deposition and impair cognition in mice displaying features of Alzheimer's disease.
- Blocking FSH action in these mice abrogates the Alzheimer's disease-like phenotype by inhibiting the neuronal C/EBPβ-δ-secretase pathway. These data not only suggest a causal role for rising serum FSH levels in the exaggerated Alzheimer's disease pathophysiology during menopause, but also reveal an opportunity for treating Alzheimer's disease, obesity, osteoporosis and dyslipidaemia with a single FSH-blocking agent.
- FSH blockade improves cognition in mice with Alzheimer's disease. Nature. 2022 Mar;603(7901):470-476. doi: 10.1038/s41586-022-04463-0. Epub 2022 Mar 2. PMID: 35236988; PMCID: PMC9940301.

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FSH – metabolic factors

- A total of 561 postmenopausal women aged 39-69 years were selected. FSH, estradiol, fasting blood glucose, and lipid profiles were analyzed. Compared with women in the highest FSH quartile, women in the lowest quartile had higher body mass index (BMI), fast blood glucose (FBG), triglyceride (TG), blood pressure, and serum estradiol (E_2) but lower high-density lipoprotein (HDL) (all $p < .05$). Compared with women in the groups of normal levels of MetS biomarkers, women in the abnormal groups had lower FSH (all $p < .01$).
- Increased quartiles of FSH were associated with significantly decreased rates of abnormal levels of metabolic factors (all $p < .05$).
- Low FSH appears to be a risk factor of all domains of MetS in postmenopausal women, which merits further study.
- Follicle-stimulating hormone associates with metabolic factors in postmenopausal women. Gynecol Endocrinol. 2018 Dec;34(12):1035-1038. doi: 10.1080/09513590.2018.1482868. Epub 2018 Jul 27. PMID: 30053787.

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FSH Levels when HRT is optimal

Women – <20 mIU/mL in women

Males 4.5 **– 7.5- 12 mIU/mL (work in progress)**

Redefining abnormal follicle-stimulating hormone in the male infertility population. BJU Int. 2012 Aug;110(4):568-72. doi: 10.1111/j.1464-410X.2011.10783.x. Epub 2011 Dec 16. PMID: 22177092.

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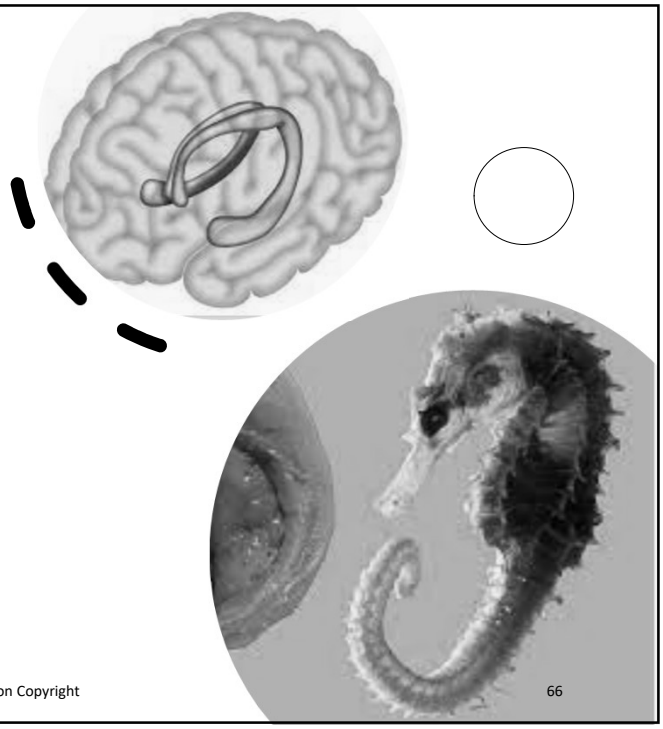
Size matters - dosing

- How the patient feels
- But also bone density
- And cognition



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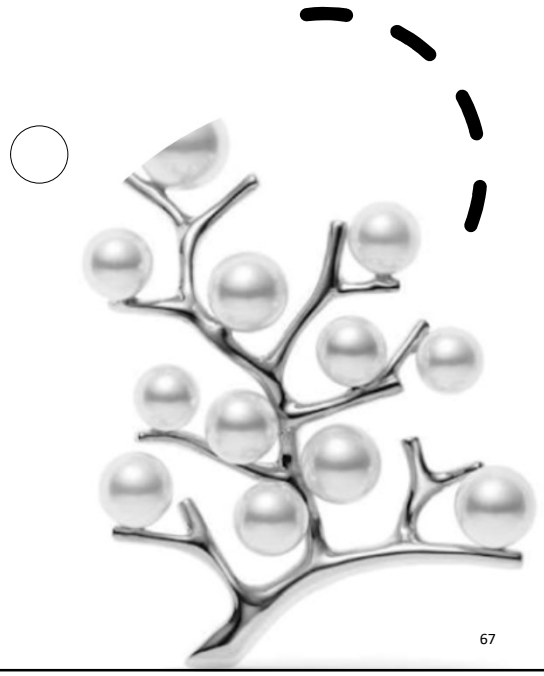
Dosing Pearls

- Be guided by how they feel
- Breast nipple tenderness, give 3 days for acclimation
- If sustained, decrease E and or increase P
- Bleeding issues usually mean too little P or too much E
- Or hormone holidays, which do not work for all or perhaps most
- Start at .25 mg of E2 .75 mg of E3 and slowly taper up
- Average woman usually needs between .8 to 2.6 estradiol equivalents
- E3 is 1/8th the potency approximately of E2



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Hormone Levels are Declining in Younger & younger

- Neuroendocrine Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA. Electronic address: fplessow@mgh.harvard.edu.
- [2]Neuroendocrine Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; Division of Pediatric Endocrinology, Massachusetts General Hospital for Children and Harvard Medical School, Boston, MA, USA.
- [3]Neuroendocrine Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA.
- [4]Child and Adolescent Psychiatry Division, Department of Psychiatry, Geneva University Hospitals and University of Geneva, Geneva, Switzerland.
- [5]Eating Disorders Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA.

- Estrogen Administration Improves the trajectory of eating disorder pathology in oligo-amenorrheic atheletes: A Randomized Trial Psychoneuroendocrinology 102 (2019) 273-280

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Hypgonadism = anxiety, depression, poor learning, worse verbal, let along bone/fertility

- Disordered eating behavior and attitudes are common in conditions of functional hypothalamic amenorrhea, such as anorexia nervosa (AN) and exercise-induced amenorrhea (Beals and Hill, 2006; Quah et al., 2009), which are also associated with significant psychiatric co-morbidity, including anxiety and depression.
- Hypogonadism in these conditions has been implicated in psychological morbidity.
- Estrogen and progesterone receptors are expressed in appetite regulation centers (e.g., the hypothalamus) and regions regulating emotion and cognition (e.g., the amygdala, ventral tegmental area, insula, and hippocampus) (Campolier et al., 2016; Coyoy et al., 2016; Minervini et al., 2015).
- In rodent and human studies, hypogonadism has been associated with cognitive dysfunction, worsening anxiety, and dysphoric mood (Baskaran et al., 2017b; Gogos et al., 2014; Lasaite et al., 2014).
- For example, hypogonadal, oligo-amenorrheic athletes show impaired verbal memory and poor cognitive control, key to successful goal-directed behavior (Baskaran et al., 2017b), and both improved after 6 months of estrogen replacement (Baskaran et al., 2017a).
- Hypoestrogenic rodents exhibit increased anxiety-related behaviors, which improved with estrogen replacement (Diz-Chaves et al., 2012; Rachman et al., 1998).
- Similarly, estrogen replacement in adolescent girls with AN reduces trait anxiety (Misra et al., 2013). While these findings highlight the close link between estrogen status and cognition, emotion, and behavior, little is known regarding the impact of hypoestrogenism on eating disorder (ED) pathology.

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Hormones Control Eating Patterns

- Ovariectomized female adult rats display increased binge eating.
- Estradiol administration (with progesterone) reversed this effect.
- Rodent study

- Ovarian hormones inhibit fat intake under binge-type conditions in ovariectomized rats. Physiol Behav. 2008 Oct 20;95(3):501-7. doi: 10.1016/j.physbeh.2008.07.021. Epub 2008 Jul 22. PMID: 18706435; PMCID: PMC2841003.

70

Oligomenorrhea

- The oligo-amenorrheic athlete, even when of normal weight, is also at increased risk for disordered eating behaviors and psychopathology.
- Bone parameters in relation to attitudes and feelings associated with disordered eating in oligo-amenorrheic athletes, eumenorrheic athletes, and nonathletes. *Int J Eat Disord* 48, 522–526.

71

Conclusion:

In OA, 12 months of estrogen replacement improves ED pathology trajectories, emphasizing the broad importance of normalizing estrogen levels.

- Examining the link between hypoestrogenism and eating behavior/attitudes and the impact of estrogen replacement in normal-weight oligo-amenorrheic athletes permits investigation of the impact of hypoestrogenism on ED pathology without low weight as a confounder and could provide a novel strategy for improving clinical care for the female athlete triad.
- We hypothesized that (1) normal-weight oligo-amenorrheic athletes would show more pronounced ED pathology compared to eumenorrheic athletes and non-athletes, and (2) 12 months of estrogen replacement would improve these symptoms.
- We focused on primary eating attitudes and behaviors underlying ED pathology, namely body dissatisfaction, drive for thinness, cognitive restraint, uncontrolled eating, and emotional eating.
- Briefly, body dissatisfaction refers to a discrepancy between perceived and desired body image, while drive for thinness represents the desire to be thinner; and both body dissatisfaction and drive for thinness represent key risk factors for developing and maintaining an ED (Beals and Hill, 2006; Stice et al., 2017; Stice and Shaw, 2002).
- Cognitive restraint represents an individual's effort to consciously limit caloric intake, uncontrolled eating is overconsumption of food accompanied by a perceived loss of control (binge eating), and emotional eating refers to eating in response to negative emotions. These three behaviors characterize the core behaviors of ED pathology.
- Estrogen administration improves the trajectory of eating disorder pathology in oligo-amenorrheic athletes: A randomized controlled trial. Psychoneuroendocrinology. 2019 Apr;102:273-280. doi: 10.1016/j.psyneuen.2018.11.013. Epub 2018 Nov 16. PMID: 30639922; PMCID: PMC6664444.

72

Girls 13 to 18 randomized trial

- The impact of estrogen replacement on anxiety, eating attitudes, and body image has not been reported in anorexia nervosa. **We hypothesized that physiologic estrogen replacement would ameliorate anxiety and improve eating attitudes without affecting body image in anorexia nervosa.**
- **Method: Girls 13-18 years old with anorexia nervosa (DSM-IV) were randomized to transdermal estradiol (100 µg twice weekly) with cyclic progesterone or placebo patches and pills for 18-months, between 2002 and 2010**. The State-Trait Anxiety Inventory for Children (STAIC), the Eating Disorders Inventory-2 (EDI-2), and the Body Shape Questionnaire (BSQ-34) were administered. 72 girls completed these measures at baseline (n=38 [girls receiving estrogen] and n=34 [girls receiving placebo]) and 37 at 18 months (n=20 [girls receiving estrogen] and n=17 [girls receiving placebo]). The primary outcome measure was the change in these scores over 18 months.
- **Results:** Estrogen replacement caused a decrease in STAIC-trait scores (-3.05 [1.22] vs. 2.07 [1.73], P=.02), without impacting STAIC-state scores (-1.11 [2.17] vs. 0.20 [1.42], P=.64). There was no effect of estrogen replacement on EDI-2 or BSQ-34 scores. Body mass index (BMI) changes did not differ between groups, and effects of estrogen replacement on STAIC-trait scores persisted after controlling for BMI changes (P=.03).
- **Increases in serum estradiol were significantly associated with decreases in STAIC-trait scores** (Spearman ρ = -0.45, P=.03).
- **Conclusions:** (the tendency to experience anxiety) but did not impact eating attitudes or body shape perception. **Estrogen replacement improved trait anxiety.**

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Premature Ovarian Failure

- 30 year old
- Intense anxiety and brain fog hard to work or go to college
- FSH was 150
- Gave Receptor Detox, Hormone Balance & Protect, pregnanolone, progesterone and within a week anxiety and insomnia were 80%.
- Added estriol reboot and within one month FSH went down to 70
- When added estrogen patch 0.025 mg lower abdomen upper buttock once/week then FSH went below 10 and young woman felt like herself again.

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Women 14 to 24 years of age on ER for 12 months

- **Objective:** Estrogen replacement prevents worsening body dissatisfaction with weight gain in adolescents with anorexia nervosa. However, the impact of estrogen administration on eating disorder (ED) pathology in normal-weight young women with exercise-induced amenorrhea is unknown. We hypothesized that (1) normal-weight oligo-amenorrheic athletes (OA) would show greater ED pathology than eumenorrheic athletes (EA) and non-athletes (NA), and (2) 12 months of estrogen replacement would improve those symptoms.
- **Trial design:** Randomized trial.
- **Methods:** One hundred seventeen OA, 50 EA, and 41 NA completed the Eating Disorder Inventory-2 (EDI-2) for measures of Drive for Thinness (DT) and Body Dissatisfaction (BD) and the Three-Factor Eating Questionnaire-R18 (TFEQ-R18).
- OA were then randomized to receive 100 mcg transdermal 17β-estradiol with cyclic progesterone (PATCH), an oral contraceptive pill (30 mcg ethinyl estradiol + 0.15 mg desogestrel) (PILL), or no estrogen (E-) for 12 months. Data are reported for the subset that completed questionnaires at 0 and 12 months between 11/2009 and 10/2016.
- **Results:** OA showed higher EDI-2 DT and TFEQ-R18 Cognitive Restraint scores than EA and NA and higher EDI-2 BD scores than EA. Over 12 months, the E+ group (PATCH+PILL), compared to E-, showed improved trajectories for EDI-2 DT and BD scores. In 3-group comparisons, PATCH outperformed E- for decreases in EDI-2 DT and BD, and the PILL for TFEQ-R18 Uncontrolled Eating.
- **Conclusion:** In OA, 12 months of estrogen replacement improves ED pathology trajectories, emphasizing the broad importance of normalizing estrogen levels.

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Oligomenorrhea – insufficient estrogen effecting cognition

- Objective: Both estrogen and exercise may have cognition enhancing benefits; however, young oligomenorrheic/amenorrheic athletes (OA) with estrogen deficiency have not been evaluated for cognitive deficits. Our objective was to determine whether 6 months of estrogen replacement will impact cognitive domains in OA. We hypothesized that estrogen replacement would improve verbal memory and executive control in OA.
- Methods: We performed cognitive assessments at baseline and after 6 months in 48 OA (14–25 years) randomized to estrogen (EST+) (oral 30 μg ethinyl estradiol [n = 16] or transdermal 100 μg 17-β-estradiol patch [n = 13]) or no estrogen (EST-) (n = 19) in an ongoing clinical trial. Neurocognitive testing included California Verbal Learning Test—Second Edition (CVLT-II) (for verbal memory) and Delis-Kaplan Executive Function System Color-Word Interference Test (D-KEFS-CWIT) (executive control).
- Results: On average, subjects (mean ± SEM age: 19.9 ± 3.1 years, body mass index: 20.6 ± 2.3 kg/m2) participated in 10.3 ± 5.9 hours per week of weight-bearing activities of their lower limbs. The EST+ group performed better for CVLT-II verbal memory scores for immediate recall over 6 months of therapy compared to EST- ($P < .05$) even after controlling for baseline scores and age. Changes in D-KEFS-CWIT scores over 6 months did not differ between the groups. However, the EST+ group had greater improvements in inhibition-switching completion time over 6 months compared with the EST- group after controlling for baseline scores and age ($P = .01$).
- Conclusions: OA show improvements in verbal memory and executive control following 6 months of estrogen replacement. These findings in athletes, who are in their prime of neurocognitive development, underscore the need for future studies exploring cognition in OA.
- **Estrogen Replacement Improves Verbal Memory and Executive Control in Oligomenorrheic/Amenorrheic Athletes in a Randomized Controlled Trial Psychiatrist.com March 14 2017**

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Hypoestrogenism - anxiety

- Hypoestrogenic rodents exhibit increased anxiety-related behaviors, which improved with estrogen replacement (Diz-Chaves et al., 2012; Rachman et al., 1998).
- Similarly, **estrogen replacement in adolescent girls with AN reduces trait anxie**ty (Misra et al., 2013).
- Impact of physiologic estrogen replacement on anxiety symptoms, body shape perception, and eating attitudes in adolescent girls with anorexia nervosa: data from a randomized controlled trial. J Clin Psychiatry. 2013 Aug;74(8):e765-71. doi: 10.4088/JCP.13m08365. PMID: 24021517; PMCID: PMC4017248.

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Increase of anxiety & Mood dysregulation/decrease endogenous hormones

- In this study, we assessed prevalence and burden estimates from GBD 2019 for 12 mental disorders, males and females, 23 age groups, 204 countries and territories, between 1990 and 2019.
- The age-standardised prevalence of eating disorders, ADHD, conduct disorder, and autism spectrum disorders was highest in high-income regions.
- **Interpretation:** GBD 2019 showed that mental disorders remained among the top ten leading causes of burden worldwide, with no evidence of global reduction in the burden since 1990.

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Incidence2019

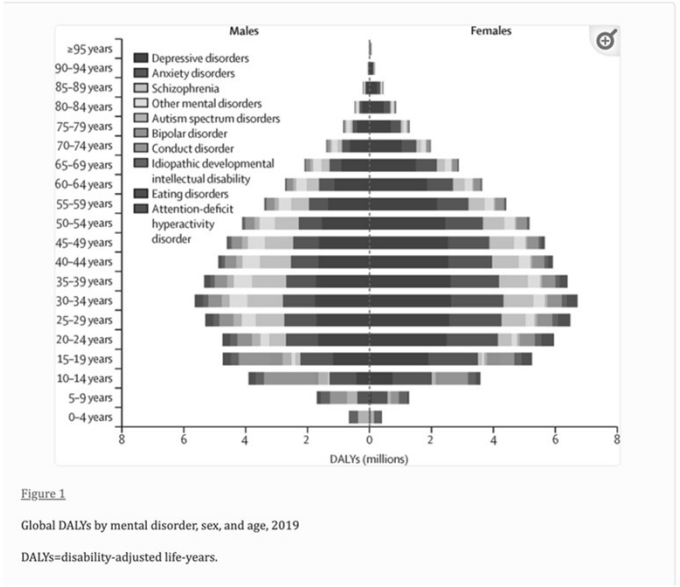

Figure 1

Global DALYs by mental disorder, sex, and age, 2019

DALYs=disability-adjusted life-years.

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The prevalence of disordered eating, menstrual dysfunction, and low bone mineral density among US collegiate athletes

- The purpose of this study was to investigate the prevalence of self-reported restrictive eating, current or past eating disorder, and menstrual dysfunction and their relationships with injuries.
- Furthermore, we aimed to compare these prevalences and associations between younger (aged 15-24) and older (aged 25-45) athletes, between elite and non-elite athletes, and between athletes competing in lean and non-lean sports. Data were collected using a web-based questionnaire.
- Participants were 846 female athletes representing 67 different sports.
- Results showed that 25%, 18%, and 32% of the athletes reported restrictive eating, eating disorders, and menstrual dysfunction, respectively.
- Higher rates of lean sport athletes compared with non-lean sport athletes reported these symptoms, while no differences were found between elite and non-elite athletes. Younger athletes reported higher rates of menstrual dysfunction and lower lifetime prevalence of eating disorders. Both restrictive eating (OR 1.41, 95% CI 1.02-1.94) and eating disorders (OR 1.89, 95% CI 1.31-2.73) were associated with injuries, while menstrual dysfunction was associated with more missed participation days compared with a regular menstrual cycle (OR 1.79, 95% CI 1.05-3.07).
- Our findings indicate that eating disorder symptoms and menstrual dysfunction are common problems in athletes that should be managed properly as they are linked to injuries and missed training/competition days.
- Self-Reported Restrictive Eating, Eating Disorders, Menstrual Dysfunction, and Injuries in Athletes Competing at Different Levels and Sports. Nutrients. 2021 Sep 19;13(9):3275. doi: 10.3390/nu13093275. PMID: 34579154; PMCID: PMC8470308.

80

Female Athletes

- The purpose of the study was to make a systematic review and describe and confront recent studies that compare the presence of disordered eating and its complications in young female athletes and controls
- Out of 169 studies 22 were selected and 11,000 women from 68 sports were studied.
- Results showed that 55% found no significant difference in the percentage of disordered eating between athletes and controls.
- Also a higher percentage of studies reported higher frequency of menstrual dysfunction in athletes than controls and finally 50% of the studies found incidence of low bone mass in controls.
- Not all the studies that investigated all the conditions in the triad, but the authors concluded that it seemed that female athletes were in more severe stage of this disorder.
- Are female athletes at increased risk for disordered eating and its complications? Appetite. 2010 Dec;55(3):379-87. doi: 10.1016/j.appet.2010.08.003. Epub 2010 Aug 13. PMID: 20709126.

81

Low estrogen in young females

- In young women, low estrogen levels complicate a wide variety of diseases, including premature ovarian failure, anorexia nervosa, athletic amenorrhea, prolactinoma, hypopituitarism, and chronic kidney disease.
- Hypoestrogenemia may also result from therapy with GnRH agonists, glucocorticosteroids, chemotherapy, and especially aromatase inhibitors.
- Or exposure to EDCs prenatally.
- All of these situations are associated with bone loss, because estrogen chronically suppresses bone resorption.

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Effects both genders

- **Background:** Bisphenol A (BPA) is a chemical produced in large volumes for use in manufacturing of consumer products and industrial applications, and an endocrine disruptor known to affect several hormonal systems. Bone produces hormones and is additionally a sensitive hormone target tissue, and is thus potentially sensitive to low doses of endocrine disruptors such as BPA, especially during development.
- **Methods:** 110 pregnant Wistar rats were gavaged with 0; 25 μg; 250 μg; 5000 μg or 50,000 μg BPA/kg bodyweight (bw)/day from gestational day 7 until weaning at postnatal day 22. The three-month-old offspring were sacrificed and right femurs collected for length measurements, geometrical measurements by peripheral quantitative computed tomography (pQCT), as well as for analyses of biomechanical properties using the three-point-bending method.
- **Results:** The femur was elongated in female offspring of dams exposed to 25 or 5000 μg BPA/kg bw/day (1.8% and 2.1%, respectively), and increased cortical thickness (4.7%) was observed in male offspring of dams exposed to 25 μg BPA/kg bw/day, compared to controls ($p < 0.005$). The biomechanical properties of the bone were not significantly altered.
- **Conclusions:** In utero and lactational exposure to the lowest BPA dose used in this study altered femoral geometry in both male and female offspring. This was observed at 25 μg BPA/kg bw/day, a dose lower than the Human Equivalent Dose (HED) applied by EFSA to set a temporary TDI (609 μg BPA/kg bw/day), and far lower than the No-Observed-Adverse-Effect-Level (NOAEL) (5000 μg BPA/kg bw/day) on which the US FDA TDI is based.
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Prenatal, egg, sperm, placenta, mother's milk

- Prenatal exposure to BPA disturbs mammary gland histoarchitecture and increases the carcinogenic susceptibility to chemical challenges administered long after BPA exposure.
- Prenatal exposure to bisphenol A promotes angiogenesis and alters steroid-mediated responses in the mammary glands of cycling rats. J Steroid Biochem Mol Biol. 2011 Oct;127(1-2):35-43. doi: 10.1016/j.jsbmb.2011.04.001. Epub 2011 Apr 14. PMID: 21513798.
- Hormone Deception Berkson DL McGraw-Hill 2000, Awakened Medicine Press 2016

84

Knowledge is power - FSH

Aging woes from too little sex steroid or too much FSH.

SEX STEROIDS

FSH

85

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FSH

- **Weight**
- **Bone**
- **Cognition**
- Menopause is associated with bone loss and enhanced visceral adiposity.
- A polyclonal antibody that targets the β-subunit of the pituitary hormone follicle-stimulating hormone (Fsh) increases bone mass in mice.
- Here, we report that this antibody sharply reduces adipose tissue in wild-type mice, phenocopying genetic haploinsufficiency for the Fsh receptor gene Fshr. The antibody also causes profound beiging, increases cellular mitochondrial density, activates brown adipose tissue and enhances thermogenesis. These actions result from the specific binding of the antibody to the β-subunit of Fsh to block its action. Our studies uncover opportunities for simultaneously treating obesity and osteoporosis.
- Blocking FSH induces thermogenic adipose tissue and reduces body fat. Nature. 2017 Jun 1;546(7656):107-112. doi: 10.1038/nature22342. Epub 2017 May 24. PMID: 28538730; PMCID: PMC5651981.

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FSH - Cognition

- Alzheimer's disease has a higher incidence in older women, with a spike in cognitive decline that tracks with visceral adiposity, dysregulated energy homeostasis and bone loss during the menopausal transition.
- Inhibiting the action of follicle-stimulating hormone (FSH) reduces body fat, enhances thermogenesis, increases bone mass and lowers serum cholesterol in mice.
- Here we show that FSH acts directly on hippocampal and cortical neurons to accelerate amyloid-β and Tau deposition and impair cognition in mice displaying features of Alzheimer's disease.
- Blocking FSH action in these mice abrogates the Alzheimer's disease-like phenotype by inhibiting the neuronal C/EBPβ-δ-secretase pathway. These data not only suggest a causal role for rising serum FSH levels in the exaggerated Alzheimer's disease pathophysiology during menopause, but also reveal an opportunity for treating Alzheimer's disease, obesity, osteoporosis and dyslipidaemia with a single FSH-blocking agent.

- FSH blockade improves cognition in mice with Alzheimer's disease. Nature. 2022 Mar;603(7901):470-476. doi: 10.1038/s41586-022-04463-0. Epub 2022 Mar 2. PMID: 35236988; PMCID: PMC9940301.

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FSH – metabolic factors

- A total of 561 postmenopausal women aged 39-69 years were selected. FSH, estradiol, fasting blood glucose, and lipid profiles were analyzed. Compared with women in the highest FSH quartile, women in the lowest quartile had higher body mass index (BMI), fast blood glucose (FBG), triglyceride (TG), blood pressure, and serum estradiol (E_2) but lower high-density lipoprotein (HDL) (all $p < .05$). Compared with women in the groups of normal levels of MetS biomarkers, women in the abnormal groups had lower FSH (all $p < .01$).
- Increased quartiles of FSH were associated with significantly decreased rates of abnormal levels of metabolic factors (all $p < .05$).
- Low FSH appears to be a risk factor of all domains of MetS in postmenopausal women, which merits further study.

- Follicle-stimulating hormone associates with metabolic factors in postmenopausal women. Gynecol Endocrinol. 2018 Dec;34(12):1035-1038. doi: 10.1080/09513590.2018.1482868. Epub 2018 Jul 27. PMID: 30053787.

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FSH - perimenopause

- **Methods:** This cross-sectional study analyzed 2121 perimenopausal women aged 40-54 years in Zhejiang Province from January 2016 to December 2018. Regression analysis was performed to assess the relationship between FSH and metabolic parameters.
- **Results:** Serum FSH had a significant inverse association with fasting plasma glucose ($P < 0.05$) and triglycerides (TG) ($P < 0.01$) in perimenopausal women.
- However, after adjusting for body mass index, there was no significant association between FSH and fasting plasma glucose. In a model fully adjusted for demographic variables, estradiol, body mass index, high-density lipoprotein, low-density lipoprotein, homocysteine, systolic blood pressure and blood viscosity, a significant association still existed between FSH and TG (standardized $\beta = -0.095$; $R^2 = 0.155$; $P = 0.002$).
- **Conclusion:** Overall, FSH is negatively associated with metabolic parameters, especially TG, in perimenopausal women.
- These results indicated that FSH might be a biomarker for the primary prevention of disorders with lipid metabolism during the menopausal period.

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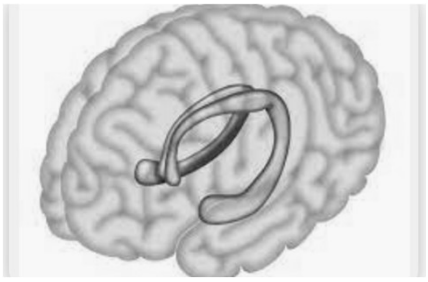
FSH - LIPIDS

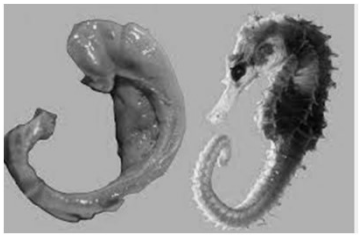
- The aim of the study was to observe the association between follicle stimulating hormone (FSH) levels and serum lipid profiles in postmenopausal women.
- A total of 411 healthy postmenopausal women with a mean age of 55 years (range 45-65 years) were enrolled in this study. Data on age, time of last menstrual period, past medical history, use of medications, and smoking status were collected, and body weight, height, and blood pressure were measured. Blood samples were collected to measure the serum concentrations of FSH, luteinizing hormone (LH), estradiol (E2), glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) using routine methods.
- FSH levels were negatively associated with LDL-C, even after adjustment for age, LH, E2, BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP) (OR = 0.185, 95% CI = 0.051-0.669).
- Although FSH may also be negatively associated with dyslipidemia ($P = .06$ for trend) and hypercholesterolemia ($P = .079$ for trend), but no statistical significance was found after adjusting for confounding factors, particularly BMI. All relevant data are within the paper and its Supporting Information files.
- The results indicated that lower FSH levels might increase the odds of dyslipidemia, especially the risk of LDL-C elevation, which is an important factor that increases the risk of CVD in postmenopausal women.
- Association of follicle stimulating hormone and serum lipid profiles in postmenopausal women. Medicine (Baltimore). 2022 Sep 30;101(39):e30920. doi: 10.1097/MD.0000000000030920. PMID: 36181065; PMCID: PMC9524973.

90

Size matters - dosing

- How the patient feels
- But also bone density
- And cognition





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Estrogen enhances hippocampal gray matter volume in young and older postmenopausal women: A prospective dose response study

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Amount of Estrogen matters for brain protection

- Estrogen administration following menopause has been shown to support hippocampally-mediated cognitive processes. A number of previous studies have examined the effect of estrogen on hippocampal structure to determine the mechanism underlying estrogen effects on hippocampal function. However, these studies have been largely observational and provided inconsistent results.
- We examined the effect of short-term estradiol administration on hippocampal gray matter volume in a prospective study with multiple doses of estradiol (placebo, 1 mg, and 2 mg).
- Following three months of estradiol administration bilateral posterior hippocampal voxel-based **gray matter volume was increased in women who received 2 mg estradiol**.
- There were no significant differences in total hippocampal volume and no significant effects on gray matter volume in women who received placebo or 1 mg estradiol. These findings accord with previous animal studies and provide evidence of estrogen effects on hippocampal morphology that may represent a neurobiological mechanism for estrogen effects on cognition in post-menopausal women.

Estrogen enhances hippocampal gray-matter volume in young and older postmenopausal women: a prospective dose-response study. Neurobiol Aging. 2017 Aug;56:1-6. doi: 10.1016/j.neurobiolaging.2017.03.033. Epub 2017 Apr 8. PMID: 28478324; PMCID: PMC5875178.

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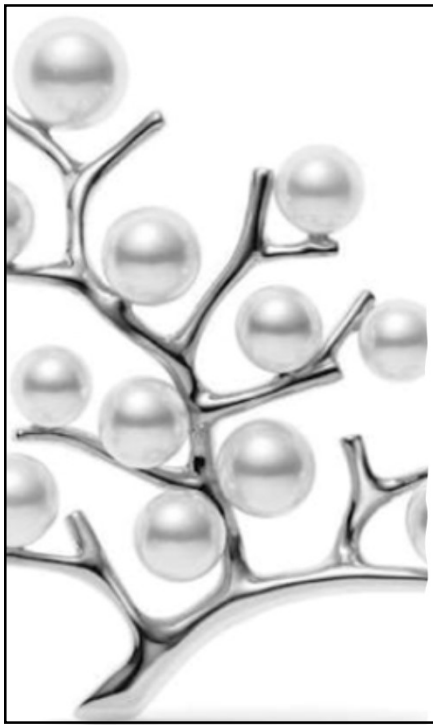

Dosing Pearls

- Be guided by how they feel
- Breast nipple tenderness, give 3 days for acclimation
- If sustained, decrease E and or increase P
- Bleeding issues usually mean too little P or too much E
- Or hormone holidays, which do not work for all or perhaps most
- Start at .25 mg of E2 .75 mg of E3 and slowly taper up
- Average woman usually needs between .8 to 2.6 estradiol equivalents
- E3 is 1/8th the potency approximately of E2

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FSH Levels when HRT is optimal

Women – <20 mIU/mL in women

Premature ovarian failure. Orphanet J Rare Dis. 2006 Apr 6;1:9. doi: 10.1186/1750-1172-1-9. PMID: 16722528; PMCID: PMC1502130.Premature ovarian failure. Orphanet J Rare Dis. 2006 Apr 6;1:9. doi: 10.1186/1750-1172-1-9. PMID: 16722528; PMCID: PMC1502130.

Males 4.5 – **7.5- 12 mIU/mL (work in progress)**

Redefining abnormal follicle-stimulating hormone in the male infertility population. BJU Int. 2012 Aug;110(4):568-72. doi: 10.1111/j.1464-410X.2011.10783.x. Epub 2011 Dec 16. PMID: 22177092.