On 8/22/19 the Chairs of the NASEM Committee on the Clinical Utility of Treating Patients with Compounded Bioidentical Hormone Replacement Therapy held a conference call with Daved Rosensweet M.D. The short conference call was held to review Dr. Rosensweet's submitted responses for research questions related to his 5/22/19 open session testimony.

cBHRT Research Questions Related to Cost; Formulations; Bioavailablity Testing; and Data on Consumer Use:

Q1: Could you provide cost estimates for the most commonly compounded formulations of bioidentical hormone replacement therapy products, as well as estimated costs for follow up testing and care?

Q2: Could you please submit data that outlines the most commonly formulated ratios of E3 to E2 and E2 to E1 in cBHRT preparations? Could you also please send supportive clinical data that reviews the efficacy and effectiveness of these commonly formulated cBHRT preparations?

Q3: It would be helpful if you can share bioavailability data (expressed as area under the curve) of E2, E3, and other hormones commonly formulated in cBHRT preparations.

Q4: The committee hopes that you are willing to submit additional evidence on the use of cBHRT. In an email, you note that "half of American women in menopause being treated with hormones are currently choosing cBHRT". Would you please send the most recent data that supports this finding? Could you also provide references that outline the demographics of current consumers of cBHRT, including measures of race/ethnicity and SES?

Below are Dr. Rosensweet's submitted responses:

Question 1: Cost Estimates

(I have repositioned the answers to this question at the end of my presentation (page 9). The data provided should be quite clear and probably will not call for questions from the Committee.)

Questions 2 &3:

- Forumations:
- Bioavailability testing:

I'd like to combine your excellent questions re Formulations (of estrogens) and Bio-availability testing and begin with important background information:

- Formulations: Women's ovaries produce three physiologically active estrogens: Estradiol (E2), Estriol (E3) and Estrone (E1)
    - cBHRT essentially began in the 1980's, and with a formulation named "Tri-Est" as it contained E2 + E3 + E1. Hormone testing soon revealed that E1 was not needed as it readily appeared on testing, interconverting from E2. "Bi-Est' has been and is the most popular of cBHRT prescribed topical estrogens.

- The originator of this formulation, an M.D. in Seattle WA, proposed the addition of Estriol to Estradiol formulations from the research of Henry Lemon M.D., an oncologist at the University of Nebraska, who published several studies in the 1960's conducted on the importance of estriol. Dr Lemon's studies demonstrated that the 24-hour urine hormone tests of women who had breast cancer (BCa) were significantly different than those of healthy women[1]:
    - Healthy women had a predominance of E3, as expressed in the mathematical formula known as the "Estrogen Quotient (EQ)" or "Estrogen Ratio:"

$$\frac{E3}{E2 + E1}$$

        - EQ of healthy women averaged 1.3
        - Women with BCa had significantly lower EQ, averaging 0.5
        - (In 2015 I was commissioned to do a study of healthy young women between the ages of 19 & 29: their average EQ was 1.1)
    - This discovery about estriol occurred decades prior to the discovery of ERβ, which is the estrogen receptor site that governs the de-proliferative phase of breast glandular tissue in the second half of a non-fertilized menstrual cycle. And, ERβ is preferentially stimulated by E3.
    - I have thorough referencing to this in the thumb drive I presented to each of you at Meeting 2, and am happy to email these references again: citations, abstracts and full articles. In the footnotes to this presentation I do include a list of references on estriol and ERβ[2-9].
- When treating with Bi-Est, various ratios of E3 to E2 are utilized. The ultimate treatment goal is to arrive at a formulation that results in a tested hormone profile that resembles the healthy EQ.
    - A most commonly prescribed *starting* formulation consists of 80% E3 + 20% E2.
        - Here is an example of an initial prescription:
            - Rx: Bi-Est 30 mg/ml 80:20 in organic oils base,
            - DTD: 8.5 ml
            - Sig: 1 – 3 drops b.i.d. as directed
                - (1 drop contains an estrogen potency equivalent to 0.44 mg of E2, designated as "0.44 mgeeq")
                - (E3 is 1/8th as potent as E2, I am happy to review the math of how mgeeq ["mg of estradiol equivalence"] a unit of estrogen potency, is determined).
            - Another example, commonly used in creams and gels:
                - Bi-Est 2.5 mg/ml in gel or cream base, 80:20, dispensed in a pump or topi-click, with one pump or click delivering ½ ml thus 0.75 mgeeq

        - (for context: average applied dose of Bi-Est in one day for a woman with good symptom relief is a range between 0.8 mgeeq to 2.4 mgeeq per day, with an average of 1.7 mgeeq/d.)

    - Variation possibilities in the ratio of E3 to E2 are multiple
        - Examples are 70:30, 60:40, 50:50,etc
        - Variations in prescription of ratios different than 80:20, in my view, should only be made when based upon the hormone testing of a woman being treated. The goal is a hormone test that results in an EQ ≥1.3, while ≤ 4.0
    - Examples will follow

- I have singled out topical administration of estrogens as best medical practice—based on the goal of minimizing risks and maximizing benefits—our medical literature describes that estrogens delivered p.o. have increased risks for alteration of coagulation profiles[10], increased breast density[11], excessive dosages leading to excessive metabolites[12], and inflammatory markers[13], among other adversities. Anyone familiar with taking medical histories on women in menopause will on occasion encounter a past medical history of deep venous thrombosis (DVT) and pulmonary embolus (PE) in a small but certain number of women suffering from same when they took oral contraceptives[14].
- Traditional and current manufactured and FDA topical estrogen products provide only E2. (Egs: patch and gels)
- And, I would like the Committee to know that I am very aware that there are a multitude of ways to treat with hormones besides cBHRT. Each method has its pros and cons, which are multiple. I am in no way advocating for the change in prescribing preferences for any good doctor. My only intention is to support the cessation of further restrictions on cBHRT. I am well aware that millions of women have benefited and been rendered safer by PremPro even, and am grateful that this has occurred over a half century of usage.

- Bio-availability data:
    - NAMS[15] has recommended and continues to recommend that hormone testing *NOT* be done on women being treated with hormones. It mentions by name "salivary" testing and "blood" testing. I absolutely agree with regards to these two particular methods.
        - My experience, and that of my most respected colleagues treating women in menopause with hormones shows that salivary testing can be erratic and too often not give data that correlates well enough with the clinical picture. (Users of this method will dispute this.)
        - Blood testing has a pharmacokinetic issue.
            - Topical administration of an ovarian hormone has variation in:
                - Rate of absorption in skin

        - Evanescence in blood levels with greater longevity in tissue levels
    - Thus, actual elapsed *time* of blood collection following previous dosage administration is:
        - Critical as to reported blood level
        - Varies considerably from woman to woman based on the absorptive ability of her skin. This absorption ability varies with health of the skin, thus younger women tend to have considerably better absorption than older women
- All issues related to pharmacokinetics disappear by doing 24-hour urine hormone testing to evaluate hormone levels in women who are being treated with hormones!
    - Correlation with the clinical symptoms of women is excellent
    - Data re parent hormones and metabolites is extensive, and relates to risks
    - Because I could never solve for the pharmacokinetic challenges of blood testing, and because I began utilizing 24-hour urine hormone testing over 20 years ago, and have thousands of test results, I cannot comment on your rightfully asked question re "bioavailability data (expressed as area under the curve)." Once a health care professional discovers 24-hour urine hormone testing, masters the required learning curve, testing issues are resolved. This is crucial: you cannot for an example, I assert, treat with the powerful hormone Insulin without proper and precise testing. Ovarian and testicular hormones are also powerful, and treatment with them should always include excellent hormone level testing.
    - Accurate testing also permits us to define optimal treatment levels as extrapolated from studies in our medical literature which clearly define what constitutes:
        - Too little estrogens: thus, leaving a woman vulnerable, for example, to bone loss and vaginal atrophy
        - Excessive estrogens: thus, vulnerability to breast glandular cell proliferation and increased breast density--a known risk factor for breast cancer.
        - Optimal testing range:

          Total Potent Estrogens (E2 + E1) = 8 – 14 mcg/24 hours

          (I have detailed in our training program the methods and references I drew from in the medical literature to determine these optimal test parameters: I'm happy to provide that process and those references upon request)
    - Cost is as low as $285
    - NAMS does not comment on this method of hormone testing.
    - (Note: I am not referring to "5-point urine hormone collections" which I do not advocate)

- Ultimate significance of Formulations and Bioavailability:
    - Re Bi-Est: because of the remarkable individual differences, woman to woman, a wide range in dosages and formulations are required. Women vary as to individual:
        - Sensitivity to any hormone you treat them with
        - Absorption and metabolization
        - Hormone level need

Below are some examples of individual patient cases, with focus on formulations of Bi-Est

D.B.		(increased mammographic breast density)	Bi-Est	Bi-Est	**Bi-Est**	**24 hour**	
date	age	Symptoms	mg/ml	E3:E2	**mgeeq**	**E2 + E1**	EQ
09/16	62	Non-significant	30	80:20	**1.8**	**20**	1.9
10/17	63	mild vaginal dryness, needs lubricant	30	80:20	**1.3**	**14**	2.5
03/19	65	mild vd, occ lube	30	80:20	**1.3**	**8.4**	3.9

- Comments:
    - Response to test results of 9/2016, with patient having TPE's (E2 + E1) a little higher than optimal @ 20 (optimal TPE's: 8 – 14 mcg/24 h) was to reduce the total dose from 1.8 mgeeq to 1.3 mgeeq as this patient had increased breast density
    - Test of 10/2017, mild symptoms were occurring: we chose to keep the dose at 1.3 mgeeq/day because of her past history of increased breast density. Test reveals an expected drop in the TPE's to 14.
    - Test of 3/2019 shows mild symptoms, with a drop to 8.4 of the TPE's: this is the first evidence of reduced absorption…a phenomenon that results from oversaturation of the skin application site, and calls for rotation to a new skin site. Note the gradual increase of the EQ…which is favorable, as we appreciate a richer level of the protective E3

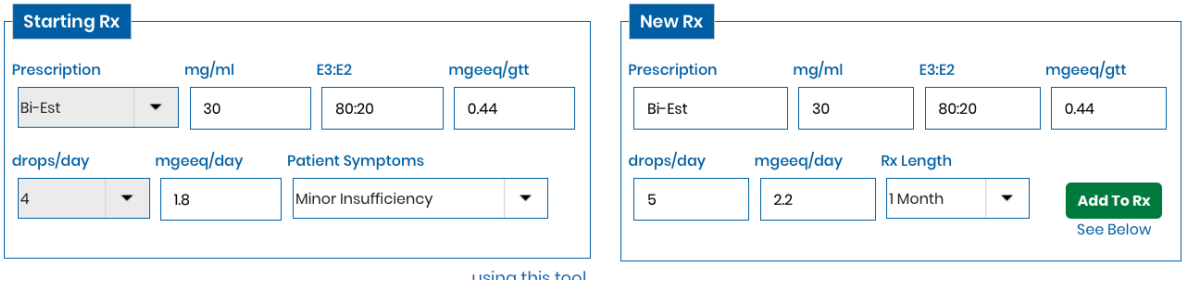
S.L.

G0 with FH of BCa & increased mammographic breast density			Bi-Est	Bi-Est	**Bi-Est**	**24 hour**	
date	age	Symptoms	mg/ml	E3:E2	**mgeeq**	**E2 + E1**	EQ
8/08	51		Vivelle 0.1	E2 only		**10.2**	0.4
4/13	55	no sx	15	80:20	0.7	**3.2**	5.2
7/15	58		15	80:20	0.9	**5.2**	2
10/16	59	occ wr, mod VD, 1 additional drop produces BT	15	80:20	1.1	**10**	3.3
3/18	60	occ awak w racing mind, mild vd, no bt	15	80:20	0.9	**2.9**	4.9
7/19	62	mild vd	30	70:30	2.8	**3.2**	3.3
8/19	-		40	70:30	3.7	**-**	-

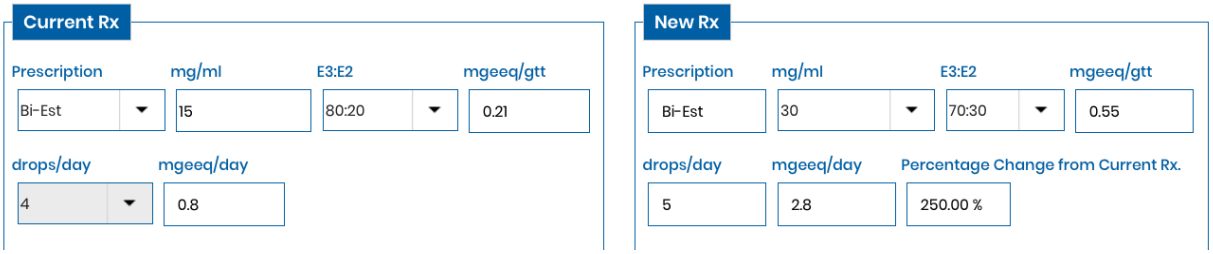
Comments:

- Note test of 8/2008: pt was on 0.1 Vivelle dot… it produced in her a TPE (E2 + E1) of 10.2…in a healthy range of 8 – 14 mcg/24h. However, the EQ was 0.4, as there is no E3 in the patch.
- Select testing dates of 2013 & 2015: low dose being used because of mammographic increased breast density along with family history of BCa. By 2016 we had gradually increased the mgeeq enough to produce a TPE of 10. This was her limit: adding one more drop per day would bring on breast tenderness—i.e., overstimulation of breast glandular tissue in this very sensitive woman.
- 2019 test: we dropped the mgeeq dose a small amount and the TPE's dropped significantly…a sign of "dermal fatigue" (reduced absorption at a specific site from saturation over time). Note that many symptoms came on with these low TPE's of 2.9. Also note that the EQ had risen above 4 to 4.9. This prompted a change in dosage and ratio, to increase the E2, the TPE's, and reduce the EQ. Note in the 2019 test she was thus on 30 mg/ml 70:30. The TPE's did respond to the increase in the mgeeq to 2.8, but only to 3.2. The EQ dropped into the optimal range: 1.3 – 4.0. Patient was having milder symptoms.
- In response to the still too low TPE's (we like it between 8 – 14 for bone and vaginal health), we increased the Bi-Est mg/ml from 30 to 40 while keeping the ratio the same.

Calculators:
To facilitate implementation of dosage changes we have produced these online calculators. (https://www.menopausemethod.com/for-medical-professionals/members-area/)



- This second calculator is for changing a Bi-Est ratio



Thus, calculation of mgeeq and even ratio changes is very easy for the trained medical professional.
Fulfilling the wide variety of mg/ml and ratios is very routine for compounding pharmacies, with their technical equipment of analytic scales and computers for calculations.

RB			Bi-Est	Bi-Est	**Bi-Est**	**24 hr TPE**	
date	age	Symptoms	mg/ml	E3:E2	**mgeeq**	**E2 + E1**	EQ
6/2016	54		15	50:50	**0.4**	**5.7**	4.6
10/2017	59	occ noc hf, mild VD, occ dyspareunia	15	50:50	**1.6**	**13**	2.3
2/2019	60	occ HF, occ ck, occ awake with racing mind, no VD	19	60:40	**2.16**	**19**	1.4
3/2019	-		30	70:30	**2.75**	**-**	-

Comments:

- Re 6/2016: (this is many years into her treatment: 15 50:50 was arrived at years ago). Low dosage had led to low TPE's. She too was nulliparous with a history of increased breast density, so year upon year we were cautious. Because TPE's of 5.7 are below threshold for risk for osteoporosis and vaginal atrophy, she titrated up her dose.
- By 10/2017 she had developed mild insufficiency symptoms: increased dosage resulted in an increase in TPE's. Because of symptoms, we increased dose again, carefully following her mammograms. We also increased the ratio and the mg/ml over time, as symptoms increased. This woman also entered menopause with an elevated SHBG, secondary to early life BCP use (relatively common) which adds complexity to her treatment regimen.

If all of this seems a bit complex:

- Medical care for any specialty you can name has a complex information base that takes years of training and experience to practice Standard of Care let alone to master. Treating women in menopause is also this complex (even though so many are practicing using a minimum of knowledge, experience, testing, etc. Our goal to the absolute best that is possible, bring to women the promise of lowest risk with maximum efficacy and elegance. Menopause Medicine *needs* to be a Boarded Specialty, and this is our major professional mission!
- These variations in prescription design, customized to each and every individual patient, is one of the many reasons to not further restrict access of women to compounding pharmacists and cBHRT.
- Please invite me back to D.C. to present live to the Committee. I promise that in two hours I can assist you so much in gaining significant deeper insight into how women in menopause are actually being treated with cBHRT. I guarantee it will bring much needed basic depth to your understanding, thus enhance your ability to make informed and wise decisions that will affect millions of American women.

Data on consumer use

I refer most often to three studies:

- A 2015 study estimates[16] that between 1 and 2.5 million women in the USA aged 40 and older use cBHRT

  [16] Compounded bioidentical hormone therapy: identifying use trends and knowledge gaps among US women. JoAnn V. Pinkerton, MD1 and Nanette Santoro, MD2. Menopause. 2015 Sep; 22(9): 926–936.
- Another 2016 study[17] estimates that somewhere between 26 to 33 million compounded prescriptions were dispensed annually, and that this number approximately equals the number of prescriptions of FDA approved menopause hormones.

  [17] Compounded non-FDA–approved menopausal hormone therapy prescriptions have increased: results of a pharmacy survey. JoAnn V. Pinkerton, MD1 and Ginger D. Constantine, MD2. Menopause. 2016 Apr; 23(4): 359–367.
- A third, and interesting study[18] was performed to determine the reasons why women were choosing cBHRT, stating "participants were attracted to CBHT because they perceive it to be (1) effective in managing menopausal symptoms (2) safer than conventional HT, (3) tailored to their individual bodies and needs, and (4) accompanied by enhanced clinical care and attention."

  [18] Why women choose compounded bioidentical hormone therapy: lessons from a qualitative study of menopausal decision-making. Jennifer Jo Thompson,1 Cheryl Ritenbaugh,2 and Mark Nichter3 BMC Womens Health. 2017; 17: 97.
- As far as demographics of these ½ of treated menopausal women, I do not have a reference for this. I can tell you about my own patient demographics over 25 years. These women tend to be:
  - Educated or highly educated
  - Very committed to their personal health
  - Have means to pay out-of-pocket. Since almost all consultation and cBHRT costs are not covered by insurance, thus are out-of-pocket, these women have the financial ability to pay. I can tell you that there is a range of this ability, from women who barely have enough to pay, but make this cBHRT a priority, to women of significant financial means.
    - I am not happy about this, and hope for the day when insurance companies see the profound preventive value of cBHRT as well as the cost savings, and covers these hormones.
- I find it very interesting when tallying up the millions and millions of cBHRT prescriptions that have been dispensed over the last 40 years, that there has been the phenomenal amount of satisfaction and the barest minimal amount of complaints, inclusive of lawsuits.

Cost Estimates

- cBHRT costs:
    - Topical preparations:
        - Bi-Est (E3 + E2), progesterone, testosterone, DHEA: $40 - $60 per Rx per month depending on the individual compounding pharmacy, bases used (oils, gels, creams), dispensing method (eg, eurobottle, pump bottle, topi-click, etc.) and if hormones are combined (if combined, price can be slightly higher).
    - Oral capsules:
        - Progesterone and DHEA: $30 - $45 per month (30 capsules), again depending upon the individual compounding pharmacy. Prices can go as high as $65/month with combinations of progesterone and DHEA, though some pharmacies do not charge for combining.
    - Total cost per month per women:
        - In the beginning there are two Rx's: Bi-Est and progesterone. Thus, costs can range from $80 - $120 per month.
        - Certainly, by three years into menopause, and possibly before, when all women's androgens (testosterone and DHEA) have fallen below acceptable and long-term health range, these two Rx's are added, with total prices increasing to $160 - $220 per month. When progesterone and DHEA are prescribed by capsule, these total costs can be reduced to as low as $140 per month. When hormones are combined, even this total can be reduced.
        - These cBHRT costs again, are almost universally out-of-pocket. I do know that rarely a specific insurance company and policy does cover these costs.
    - In general, pharmacies that maintain active licenses in multiple states (eg, even up to as high as 45 states) tend to charge the higher amounts in these ranges.

- Testing costs:
    - Hormone testing: I only do and recommend 24-hour urine hormone testing, which is $285 - $360 per most common test panel. At times these are reimbursed by the patient's insurance.
        - Add-ons are possible, I rarely do them.
        - I do not recommend any other hormone testing methods, including blood, saliva and urinary "five point."

- Blood testing:
    - SHBG and four basic Thyroid hormones are required routine in our method (above and beyond basic testing, (such as CBC, CMP, lipids, etc, based on the needs of the individual patient).
    - These are most often covered by patient's insurance.
- Mammography and Bone Density are required routine.
    - Rate of re-test is individualized to the patient
    - These are covered by insurance
- Ancillary testing, at times, indicated, such as:
    - Transvaginal uterine ultrasound (TVUS) is covered by insurance.
    - Breast thermography (good for identifying the increased heat of inflammation—and NOT for cancer screening) is approx. $180, out-of-pocket.

- Consultation costs:
    - I can give you estimates of ranges of consultation costs. These will be based on my fees and approximations of fees charged by physicians, nurse practitioners, and physician assistants that we train and mentor.
    - First year:
        - Requires an initial consultation lasting between 1 and 2 hours.
        - Follow-up consultations. Are shorter—approx ½ hour—and there are most commonly 2 – 3, and sometimes, in complex cases, additional.
        - I have seen two types of fee structures:
            - One that comes down to an hourly fee ranging from $150 - $400 per hour, and will amount to from 2.5 – 6 hours in the first year. My hourly fee: $240/hour.
            - A second "flat fee" covering all first-year consultations, ranging from $1,500 to $3,000. My fee, $2,400 for all first-year consultations, with no limit to the number or time of them.
        - These charges are commonly out-of-pocket by cBHRT providers, though a certain small percentage of them do bill insurance.
        - This is not counting the initial female exam, most commonly performed by the patient's personal gynecologist or other licensed healthcare provider. These exams are most often covered by the patient's insurance.
        - Thus, an approximate range for first year consultations can be estimated at $800 - $3,000.
    - Annual Follow-up visits:
        - These are preceded by a questionnaire, blood, hormone testing, and, depending on personal situation, mammogram, bone density, and, less commonly, TVUS, and breast thermography. These are most often covered by the patient's insurance, with the possible exception of the 24-hour hormone test (which may or may not be reimbursed by the patient's insurance) and, if needed, breast thermography, which is out-of-pocket.

- These are accompanied by a routine Annual Female Exam, most commonly performed by the patient's personal gynecologist or other licensed healthcare provider. These exams are most often covered by the patient's insurance.
- Annual consultation with a cBHRT physician, nurse practitioner or physician's assistant:
    - These are most often, though not always, out-of-pocket expenses billed by the hourly rate mentioned above, or by a flat rate.
    - There is usually only one of these annual consultations, and they range in length, most commonly, between 1 and 1.5 hours, especially when all exams and testing requested are performed prior to this annual visit.

References:

[1] **Reduced estriol excretion in patients with breast cancer prior to endocrine therapy.** Lemon HM; Wotiz HH; Parsons L; Mozden PJ. Journal of the American Medical Association. June 27, 1966; 196(13):112-120.

Abstract:

24 hour urinary estriol excretion quotients (Eq) were measured in a group of 148 collections of 64 breast cancer or precancer patients (182 specimens) and 34 controlled abnormally menstruating young women without breast cancer, normally menstruating women free of cancer and from healthy and diseased postmenopausal women without breast cancer at University Hospital in Boston. As an index of the ratio of non-carinogenic impeded estrogens to mammary carcinogenic estrogens there was some tendency to select urines from patients early in the disease. An attempt was made when frozen urines were analyzed to select control and cancerous specimens that had been frozen for equivalent time periods. Based on literature studies, .7 was considered the low normal Eq limit in premenopausal women and 1.0 for postmenopausal or postcastration women. No major differences in Eq were noted from the proliferative and the secretory phases of the menstrual cycle. 2 of the normally menstruating control women showed subnormal Eq and 1 had an excessively high Eq. Single analyses from the postmenopausal showed a mean Eq of 3.2. Previously oopherectomized women had mean values of 7.8 and 3 patients with well-compensated cardiovascular disease had Eq's of 5.4 to 8.8. 3 patients with premalignant breast or uterine pathology had subnormal Eq value. Oopherectomized women with recurrent breast cancer had lower Eq values than the oopherectomized controls. Pre-and postmenopausal patients with proven breast cancer excreted 30-60% less estriol per 24 hours than the control population. The daily excretion of estione and estradiol was similar in both groups. 24 controls and patients matched in pairs by age and ovarian status in the Wilcoxon test indicated that the decreased Eq excretion in untreated cancer was significant at the 2% level. Endocrine therapy led to a rise in Eq. Major breast or abdominal surgery led to an increased Eq. It is suggested that a disproportionately large number of subnormal estriol excretors may develop precancerous or malignant tumors.

[2] ***Differential Regulation of Estrogen Receptor (ERα) and ERβ in Primate Mammary Gland*** Guojun Cheng, et. al. The Journal of Clinical Endocrinology & Metabolism 90(1):435–444. 2005

[3] ***Estrogen Receptor β Binds to and Regulates Three Distinct Classes of Target Genes.*** *J Biol Chem.2010 Jul 16;285(29):2205966 Omar I. Viva, et. al.*

[4] ***Loss of ERβ expression as a common step in estrogendependent tumor progression.*** Bardin, et. al., Endocrine related Cancer. *Review article*. 2004 Sep; 11(3). 537 551.

[5] ***Estrogen Receptors Alpha (ERα) and Beta (ERβ): SubtypeSelective Ligands and Clinical Potential*** Ilaria Paterni, et al, Steroids. 2014 Nov 15;

[6] ***The role of estrogen receptor beta (ERbeta) in malignant diseasesa new potential target for antiproliferative drugs in prevention and treatment of cancer.*** Warner M, Gustafsson JA. Biochem Biophys Res Commun. Review article. 2010 May 21;396(1):636.

[7] ***Quantitative StructureActivity Relationship of Various Endogenous Estrogen Metabolites for Human Estrogen Receptor α and β Subtypes: Insights into the Structural Determinants Favoring a Differential Subtype Binding***. Endocrinology Zhu et al. September 2006 147 (9): 4132.

[8] ***Bedside to bench to bedside research: Estrogen receptor beta ligand as a candidate neuroprotective treatment for multiple sclerosis.*** Noriko Itoh, Rhonda R. Voskuhl, M.D. et. al. Journal of Neuroimmunology Accepted 28 September 2016.

[9] ***The Bioidentical Hormone Debate: Are Bioidentical Hormones (Estradiol, Estriol, and Progesterone) Safer or More Efficacious than Commonly Used Synthetic Versions in Hormone Replacement Therapy. Review Article***. Postgrad Med 2009;121(1):113. Holtorf K.

[10] **Postmenopausal hormone replacement therapy increases coagulation activity and fibrinolysis.**

ArteriosclerThromb Vasc Biol. 2000 May;20(5):1404-9. Teede HJ[1], McGrath BP, Smolich JJ, Malan E, Kotsopoulos D, Liang YL, Peverill RE.

Abstract: Hormone replacement therapy (HRT) appears to be cardioprotective in postmenopausal women; however, concerns exist over its thrombogenic effects. To address the effects of combined HRT on coagulation and fibrinolysis, we have measured circulating markers of these processes in a double- blind placebo-controlled trial. Forty-two healthy postmenopausal women aged 50 to 75 years received continuous combined HRT with 2 mg estradiol+1 mg norethisterone or placebo for 6 weeks. Hormone profiles were measured at baseline, and lipid and hemostatic parameters were measured at baseline and after 6 weeks of therapy. Baseline characteristics were similar in the 2 groups. With change from baseline the main outcome measure, HRT increased the markers of coagulation (prothrombin fragments 1+2, 0.20+/-0.06 versus 0.06+/-0.04 nmol/L, P=0.0005; soluble fibrin, 2.3+/-0.4 versus 0.25+/-0.3 microgram/mL, P=0.0004), reduced plasma fibrinolytic inhibitory activity (plasminogen activator inhibitor-1, -0.67+/-0.16 versus 0.24+/-0.21 U/mL, P=0.002), and increased fibrinolysis (D-dimer, 24+/-12 versus -6+/-8 ng/mL, P=0.04) compared with placebo. Increases in soluble fibrin and D-dimer were positively correlated (r=0.59, P=0.02), but changes in plasminogen activator inhibitor-1 and D-dimer were unrelated. Although baseline hemostatic and lipid parameters were correlated, there were no associations between changes in hemostatic markers and lipids after treatment. Short-term oral combined continuous HRT (estradiol and norethisterone) increased thrombin and fibrin generation, reduced plasma fibrinolytic inhibitory activity, and increased fibrinolysis. Enhanced fibrinolysis was related to increased fibrin generation but not reduced plasma fibrinolytic inhibitory activity. Coagulation activation may partly explain the increases in venous thrombosis and cardiovascular events reported with the use of combined HRT.

[11] ***Hormone replacement therapy and breast density changes.*** **Climacteric. 2005 Jun;8(2):185-92.** J Harvey1, C Scheurer2, FT Kawakami2, E Quebe-Fehling2, P Ibarra de Palacios2 and VV Ragavan. University of Virginia, USA

Objectives: To compare the incidence of increased breast density and tenderness in postmenopausal women associated with transdermal (Estalis/Combipatch®, Novartis, Basel, Switzerland) and oral (Kliogest®, Schering AG, Berlin, Germany) hormone replacement therapy (HRT).

Methods: A total of 202 postmenopausal women were randomized to transdermal or oral HRT. Mammograms obtained at study entry and after 1 year of treatment were assessed for percent breast density by means of the digital segmentation and thresholding technique. Breast tenderness was assessed at each study visit.

Results: The mean breast density by ANCOVA after adjusting for screening value at study end was significantly lower for women using Estalis® (38.4%, standard error 0.9%) compared with Kliogest® (46.9%, standard error 1.5%) ($p < 0.0001$). Significantly fewer women using transdermal HRT had an increase in mammographic breast density or breast tenderness compared to oral HRT. Of the women using transdermal HRT, 39.1% had no change in breast density compared to 15.7% for women using oral HRT. Only 4% of women using transdermal HRT had a marked increase in density (> 25%) compared to 15.7% of women using oral HRT. Overall, 36.0% of patients in the transdermal group reported breast tenderness at some point during the 1-year study, compared with 57.6% in the oral HRT group ($p = 0.0002$).

Conclusion Transdermal HRT use is associated with a significantly lower incidence of increased mammographic breast density and breast tenderness compared with oral HRT.

[12] **Hormone Replacement with Estradiol: Conventional Oral Doses Result in Excessive Exposure to Estrone** Patrick N. Friel, BS; Christa Hinchcliffe, ND; Jonathan V. Wright, MD Altern Med Rev 2005;10(1):36-41 Abstract BACKGROUND: There is a lack of consensus about the safety of estrogen replacement therapy, especially with regard to its impact on a woman's risk for breast cancer. Elevated urinary or serum estrone and estradiol concentrations in postmenopausal women are associated with a moderately elevated risk of breast cancer. METHODS: Twenty-four-hour urinary steroid hormone profiles, including the measurement of estrone, estradiol, and estriol, were conducted for 35 postmenopausal women receiving oral estradiol at doses from 0.025-2.0 mg/day. RESULTS: Urinary excretion of estradiol exceeded premenopausal reference range values in women taking estradiol at doses greater than 0.5 mg/day. Urinary estrone excretion exceeded premenopausal reference range values in women taking estradiol doses of 0.25 mg/day or higher. Literature data indicate serum estrone concentrations also markedly exceed premenopausal reference ranges when estradiol is administered orally at a dose of 1 mg/day. CONCLUSIONS: The previously recommended oral dose of estradiol (1-2 mg/day) results in urinary excretion of estrone at values 5- 10 times the upper limit of the reference range for premenopausal women. Retrospective studies associating oral estradiol with increased risk of breast cancer may reflect overdose conditions. Based on current knowledge, a prudent dose ceiling for oral estradiol replacement therapy of 0.25 mg/day is proposed.

[13] **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**. Kenna Stephenson, MD, International Journal of Pharmaceutical Compounding Vol. 17 No. 1 | January/February 2013FAAFPThe 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. Seventy-five women who met strict inclusion/exclusion criteria were enrolled....hormone therapy of BiEst (80%Estriol/20%Estradiol), and/or Progesterone for eight weeks...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.

[14] Oral Estradiol package insert (PDF): https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/081295s014,084499s042,084500s044lbl.pdf

[15] "Testing hormone levels is not required to determine whether a woman has the "right amount" of hormones. How symptoms respond to a particular dose of hormones or nonhormonal menopause medication is the only reliable guide" from https://www.menopause.org/publications/clinical-practice-materials/bioidentical-hormone-therapy/what-is-hormone-testing-

[16] Compounded bioidentical hormone therapy: identifying use trends and knowledge gaps among US women. JoAnn V. Pinkerton, MD1 and Nanette Santoro, MD2. Menopause. 2015 Sep; 22(9): 926–936.

[17] Compounded non-FDA–approved menopausal hormone therapy prescriptions have increased: results of a pharmacy survey. JoAnn V. Pinkerton, MD1 and Ginger D. Constantine, MD2. Menopause. 2016 Apr; 23(4): 359–367.

[18.] Why women choose compounded bioidentical hormone therapy: lessons from a qualitative study of menopausal decision-making. Jennifer Jo Thompson,1 Cheryl Ritenbaugh,2 and Mark Nichter3 BMC Womens Health. 2017; 17: 97.