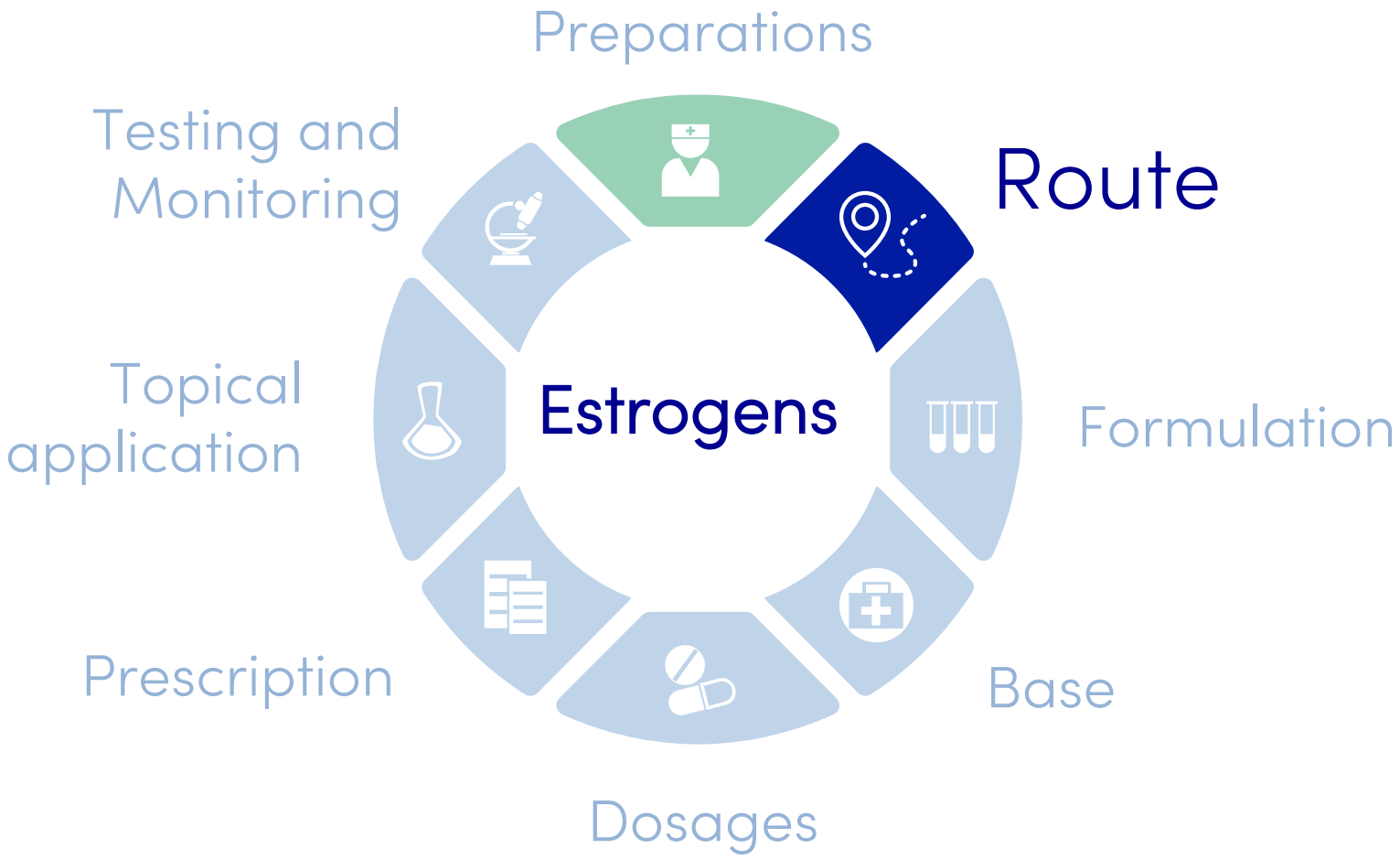

Preparations
Route
Formulation
Base
Dosages
Prescription
Topical application
Testing and Monitoring
Estrogens

Right Estrogen Route:

What is it?

Optional administration routes of Estrogens

Transdermal — Compounded organic oils base, or gels & creams

New Pharmaceutical Products

Transmucosal preparations:

Estriol Bi-est progesterone testosterone DHEA

trans-labial, trans-vaginal, trans-external peri-anal mucosa

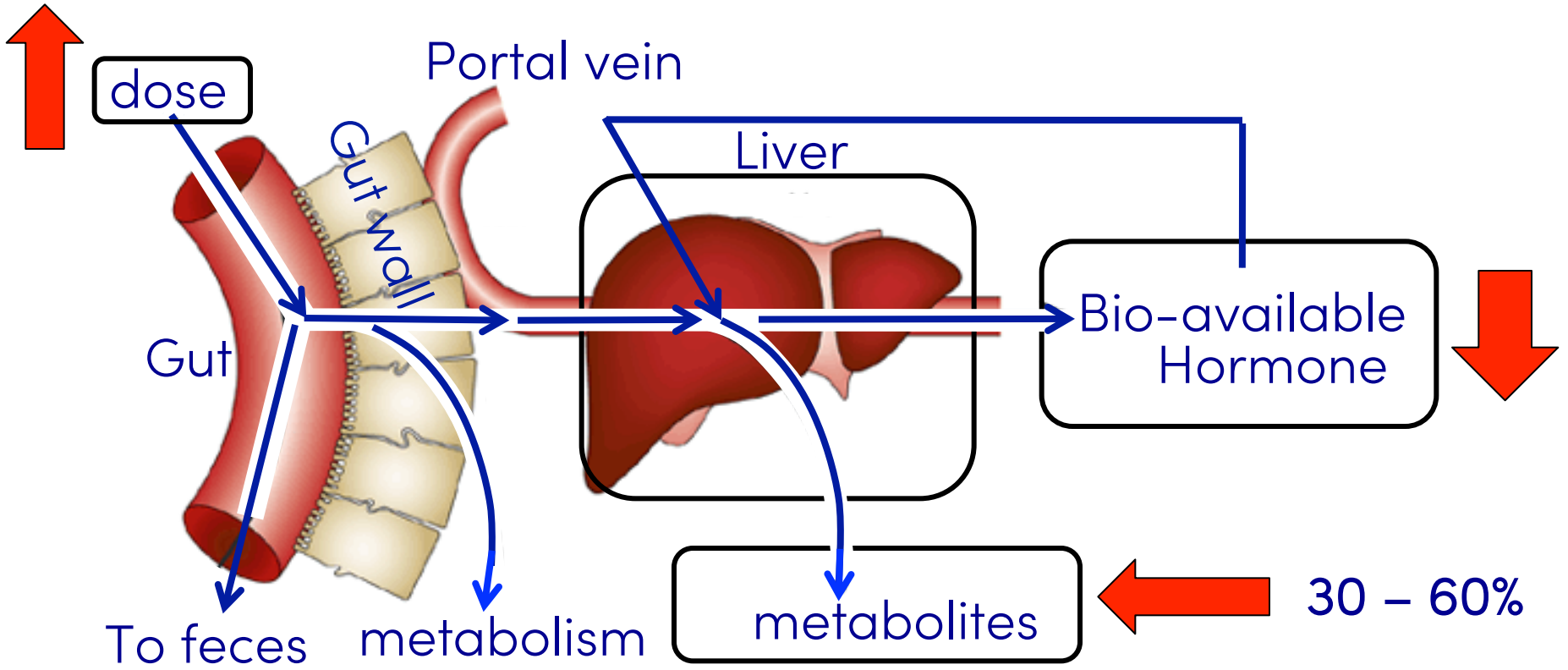
Patch — Dermal patch is 'bio-identical' [+] estradiol

0.025, 0.05, 0.075, 0.1 mg *[*dose "delivered"]*

Sublingual? — Bi-est & Estradiol

Oral Estrogens — **safety issues**

"First pass through the liver"



Outcomes:

- Metabolite levels are remarkably elevated
- Bio-available hormone levels are reduced/dose given
- higher oral dosages are required to achieve adequate plasma concentrations of hormones

Hormone replacement therapy and breast density changes

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.
Climacteric. J Harvey, C Scheurer, et al. 2005 Jun;8(2):185-92. 2005, Vol. 8, No. 2 , Pages 185-192

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

Are all estrogens created equal? A review of oral vs. transdermal therapy

Abstract

BACKGROUND:

To compare oral and transdermal delivery systems in domains of lipid effects; cardiovascular, inflammatory, and thrombotic effects; effect on insulin-like growth factor, insulin resistance, and metabolic syndrome; sexual effects; metabolic effects including weight; and effects on target organs bone, breast, and uterus. METHODS:

Review of the literature 1990-2010. Studies selected on basis of applicability, quality of data, and relationship to topic. RESULTS: Data applicable to the comparisons of oral versus transdermal delivery systems for postmenopausal estrogen therapy were utilized to perform a review and formulate conclusions.

CONCLUSIONS:

Significant differences appear to exist between oral and transdermal estrogens in terms of hormonal bioavailability and metabolism, with implications for clinical efficacy, potential side effects, and risk profile of different hormone therapy options, but neither results nor study designs are uniform. Bypassing hepatic metabolism appears to result in more stable serum estradiol levels without supraphysiologic concentrations in the liver. By avoiding first-pass metabolism, transdermal hormone therapy may have less pronounced effects on hepatic protein synthesis, such as inflammatory markers, markers of coagulation and fibrinolysis, and steroid binding proteins, while oral hormone therapy has more pronounced hyper-coagulant effects and increases synthesis of C-reactive protein and fibrinolytic markers. Both oral and transdermal delivery systems have beneficial effects on high-density lipoprotein cholesterol to low-density lipoprotein cholesterol ratios (oral>transdermal), while the transdermal system has more favorable effects on triglycerides. Incidence of metabolic syndrome and weight gain appears to be slightly lower with a transdermal delivery system. Oral estrogen's significant increase in hepatic sex hormone binding globulin production lowers testosterone availability compared with transdermal delivery, with clinically relevant effects on sexual vigor.

Goodman MP. J Womens Health (Larchmt). 2012 Feb;21(2):161-9. doi: 10.1089/jwh.2011.2839. Epub 2011 Oct 19.

Are all estrogens created equal?
A review of oral vs. transdermal therapy

Significant differences appear to exist between oral and transdermal estrogens....

Bypassing hepatic metabolism Transdermal hormone Rx:

- appears to result in more stable serum estradiol levels without supraphysiologic concentrations in the liver.

May have less pronounced effects on hepatic protein synthesis, such as:

- inflammatory markers, [eg. C-reactive protein]
- markers of coagulation and fibrinolysis, and steroid binding proteins, [eg. SHBG, which lowers testosterone availability, thus libido]

Coagulation issues matter!

Remembering.....

- Women's age-adjusted mortality rates from heart disease are four to six times higher than their mortality rates from breast cancer.*

*Coronary Artery Disease Prevention: What's Different for Women? J Bedinghaus M.D. L LeShan M.D.et, al. Medical College of Wisconsin, Milwaukee, Wisconsin Am Fam Physician. 2001 Apr 1;63(7):1393-1401.

- The main issue with atherosclerotic coronary arteries is that they are a nidus for clot.

See Appendix 1a: Coagulation, Atherosclerosis

Back to ‘First Pass’.....

Let me Illustrate:

24 hour urine hormone testing instructions:

- “Take all hormones you are using before & during the 24 hour urine collection period”
- “EXCEPTION:”

  “If you are taking hormones orally, OMIT taking them
  - the night prior to beginning urine collection plus
  - during the urine collection period”

55 yowf, thin, severely symptomatic: prior failures with TD, patch, vaginal, anal application

24 hr urine hormone test:
(Rx ref range: 750-1500)

Prep	Route	mg h.s.	PD**
Progesterone	T.D.	38	338
Progesterone	P.O.*	75	9565***

* Omitted night prior to collection, took it the night during collection

**Pregnanediol is the principle metabolite of Progesterone

***Oral progesterone dosages: 95 – 98% administered goes through first-pass. PD is approx 15-25% derived from circulating progesterone (not first pass)

55 yowf, thin, severely symptomatic: prior failures with TD, patch, vaginal, anal application

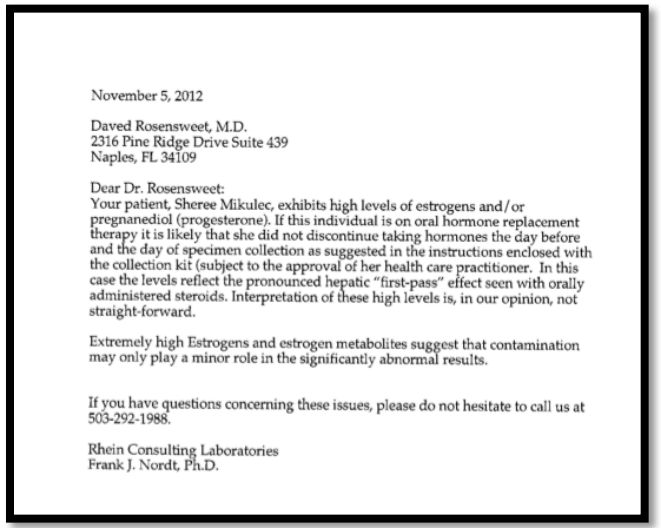
24 hr urine hormone test:

Prep	Route	mgeeq/ 24h	8 - 14 TPE's	2-4 Eq
Bi-est	T.D.	2.3	3.3	4.2

Get ready for CRAZY!!!

E2	P.O.*	4	1081	0.1

* TAKEN night before + during 24 hour urine collection



November 5, 2012

Daved Rosensweet, M.D.
2316 Pine Ridge Drive Suite 439
Naples, FL 34109

Dear Dr. Rosensweet:
Your patient, Sheree Mikulec, exhibits high levels of estrogens and/or pregnanediol (progesterone). If this individual is on oral hormone replacement therapy it is likely that she did not discontinue taking hormones the day before and the day of specimen collection as suggested in the instructions enclosed with the collection kit (subject to the approval of her health care practitioner. In this case the levels reflect the pronounced hepatic "first-pass" effect seen with orally administered steroids. Interpretation of these high levels is, in our opinion, not straight-forward.

Extremely high Estrogens and estrogen metabolites suggest that contamination may only play a minor role in the significantly abnormal results.

If you have questions concerning these issues, please do not hesitate to call us at 503-292-1988.

Rhein Consulting Laboratories
Frank J. Nordt, Ph.D.

Oral Estradiol:
Increased Hormone & Metabolite Issues

Conclusion: 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 0.25mg/day is proposed.

Wright, JV, Friel, P, Hinchcliffe, C: Hormone Replacement with Estradiol: Conventional Oral Doses result in Excessive Exposure to Estrone. Alternative Medicine Review: Vol 10, Num 1 2005

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 [sic: if it is to be ever used] estradiol replacement therapy of 0.25mg/day is proposed.

Transdermal vs Oral Estrogen: Another Resource

- Since there is no first-pass liver deactivation of transdermal estradiol, effective doses are small. First-pass metabolism of oral estradiol is associated with adverse events traditionally attributed to menopausal hormone therapy. First pass significantly impairs bioavailability of oral estradiol. Large doses required to overcome first pass induce supraphysiologic release of hepatic proteins, including C-reactive protein (CRP), insulin-like growth factor 1, clotting factors, and hormone-binding globulins (ie, sex hormone–binding globulin [SHBG], thyroxine-binding globulin [TBG], and cortisol-binding globulin [CBG]). 1-3 First pass impacts adversely on lipids, cardiovascular functions, inflammatory and thrombotic mechanisms, insulin resistance, and weight control, and it may aggravate metabolic syndrome.

John E. Buster, MD Professor of Obstetrics and Gynecology,The Female Patient. 2010:35(9):24-27
http://www.femalepatient.com/html/arc/sig/meno/articles/035_09_024.asp

Transdermal vs Oral Estrogen: Poignancy

Since there is no first-pass liver deactivation of transdermal estradiol, effective doses are small.

First-pass metabolism of oral estradiol is associated with adverse events traditionally attributed to menopausal hormone therapy..

First pass significantly impairs bioavailability of oral estradiol. Large doses required to overcome first pass induce supraphysiologic release of hepatic proteins, including C-reactive protein (CRP), insulin-like growth factor 1, clotting factors, and hormone-binding globulins (ie, sex hormone–binding globulin [SHBG], thyroxine-binding globulin [TBG], and cortisol-binding globulin [CBG]).1-3

First pass impacts adversely on lipids, cardiovascular functions, inflammatory and thrombotic mechanisms, insulin resistance, and weight control, and it may aggravate metabolic syndrome.

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

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. 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.

Kenna Stephenson, MD, FAAFP et. al., International Journal of Pharmaceutical Compounding, Vol 17 No. 1, January/February 2013 www.IJPC.com

The Effects of Compounded Bioidentical Transdermal Hormone ....

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Don't Become a Victim of All-Too-Common Errors in Bioidentical Hormone Replacement Therapy

Fundamental Error #1

Swallowing Estrogen

Jonathan V. Wright M.D.

Townsend Letter December 2013,
365: 59 - 62

Right Estrogen Route:
Transdermal or Transmucosal
- not oral -