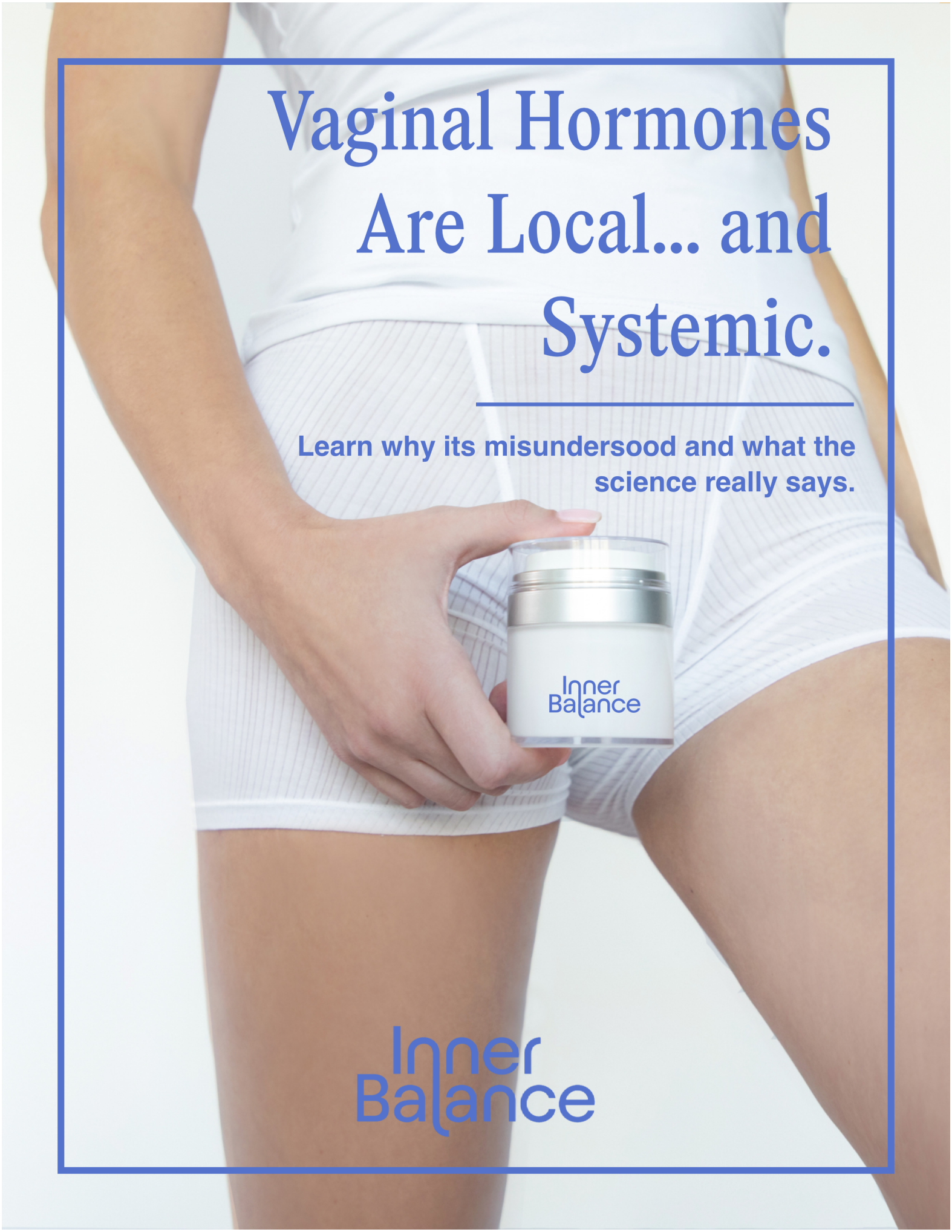

Vaginal Hormones Are Local... and Systemic.

Learn why its misundersood and what the science really says.

Inner Balance

The quick takeaway
Vaginal delivery bypasses first-pass liver metabolism and can deliver medications into the bloodstream. ***That's systemic.***

Many "vaginal estrogen" products and studies focus on *very low-doses* -- designed only for vaginal dryness. Those **microdoses aim for minimal systemic levels**—so papers about those products often say "not systemic." ***That's a design choice, not a limit of the vaginal route.***

When you use ***adequate doses or whole-body-purpose formulations***, hormones given vaginally ***do appear in the blood*** and can reach target tissues. Multiple pharmacokinetic studies show this with estradiol, progesterone, and combined hormonal contraceptive rings.

Why the vaginal route can be systemic
The vaginal wall is richly supplied with blood vessels, and drains into pelvic veins that lead directly to the blood circulation—***no gut, no first-pass liver detour, no liver burden***. That can mean steady blood levels with less stomach upset and (for some drugs) lower dose requirements than oral. Reviews in gynecology and pharmacology have highlighted these advantages for decades.

There's also a phenomenon called the "***first uterine pass effect***." Some drugs placed in the upper vagina can preferentially reach the uterus before diffusing elsewhere—useful when targeting the uterus—but it doesn't negate systemic absorption; it simply means both uterine targeting and systemic exposure can occur.

Why so many papers say vaginal is "not systemic"
A lot of widely cited research (and clinical guidance) evaluates low-dose vaginal estradiol products meant only for genitourinary syndrome of menopause (GSM)—think 10–25 μg estradiol tablets, low-dose creams, or local rings. *These are* ***intentionally formulated to minimize blood levels*** *while restoring vaginal tissues.* So, when those trials report "minimal systemic absorption," they're confirming those microdose designs worked as planned—*not proving the vaginal route can't be systemic.*

A good example: a large analysis of a **10 μg** vaginal estradiol tablet showed only small increases in serum estradiol compared with placebo—again, because the dose is tiny and intended to be local.

Evidence that vaginal hormones reach the bloodstream
Estradiol
Head-to-head studies: When estradiol is given vaginally (at therapeutic doses), researchers have measured serum estradiol and endometrial tissue levels consistent with systemic exposure—thanks to local uptake and strong blood flow.

Dose matters: A review synthesizing multiple products found dose-dependent systemic absorption—***lower doses = lower blood levels, higher doses = higher blood levels***—*which is exactly what you'd expect if the route is capable of being systemic.*

Progesterone
Vaginal progesterone (e.g., Crinone® 8%) *are used in fertility care* precisely because they yield ***measurable serum progesterone and effective endometrial exposure***. Classic pharmacokinetic comparisons versus oral progesterone show **reliable circulating levels after vaginal dosing. FDA labeling and clinical trials document serum levels for vaginal progesterone.**

Vaginal progesterone (e.g., Crinone® 8%) results in greater bioavailability with less serum variability than oral progesterone. Therefore ***vaginal delivery provides more reliable delivery of progesterone, compared with oral progesterone.***

Topical progesterone: studies consistently show that *topical progesterone delivers very low serum levels*—often well below luteal phase concentrations. For example, in postmenopausal women using 30–80 mg cream, serum progesterone rarely exceeded 1 ng/mL.

Oral, vaginal (Crinone), and vaginal systemic-target (Oestra) routes achieve much higher systemic levels than topical.

Combined contraceptive vaginal rings
Products like the etonogestrel/ethinyl estradiol vaginal ring prevent pregnancy by maintaining systemic hormone levels; their labels report steady serum etonogestrel and ethinyl estradiol concentrations. The fact that a vaginal ring can reliably suppress ovulation systemically is direct, *everyday evidence of systemic delivery via the vaginal route.*

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Putting the pieces together

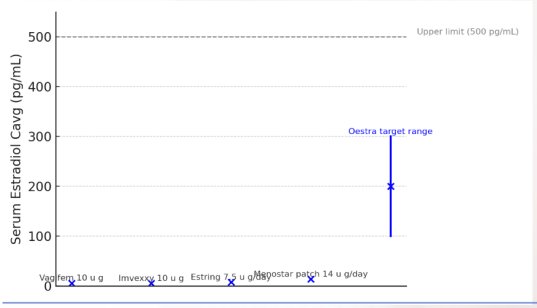
- ✔ *Biological evidence* supports uptake from the vagina into the blood.
- ✔ *Pharmacokinetics confirm* estradiol and progesterone placed vaginally show up in blood tests—with levels that scale by dose and formulation.
- ✔ *Everyday contraceptive use* (vaginal rings) proves the point in millions of users: vaginal delivery can maintain systemic drug levels consistently enough to work.
- ✔ So, when you read that "vaginal delivery isn't systemic," *check which dose is being used*. If it's a very low-dose the goal is minimal systemic absorption—by design. ***That does not generalize to "vaginal is not systemic."***

***Oestra™ is systemic on purpose*. Here is why it makes sense:**
Bypasses first-pass liver metabolism: Potential for lower milligram doses than oral, less toxic metabolites, less burden on the liver, and less estrone is made.

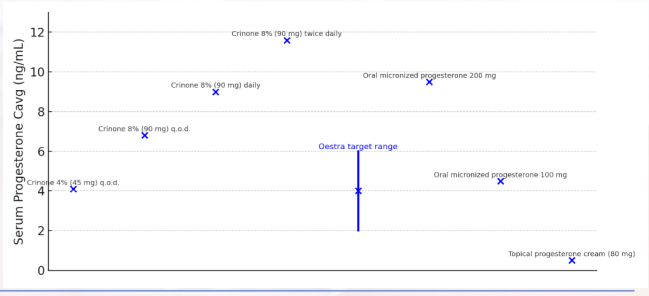
Stable levels: Sustained release and steadier concentrations across 24 hours.
Targeted uterine exposure + systemic delivery: The first uterine pass effect can enhance uterine exposure (progesterone) while still allowing hormones into the blood stream.

Bioavailability: Vaginal delivery provides a higher proportion of the active, usable form of both hormones, with less conversion to unwanted estrone. *For estrogen, about 70% of what's absorbed vaginally is active (unconjugated) compared to 35% with oral dosing.*
Even if overall blood levels are lower than oral therapy, vaginal delivery can be more efficient at supplying the beneficial form your body needs while minimizing less useful forms.

Estradiol Serum Levels by Product*



Progesterone Serum Levels by Product*



What this means if you're considering Oestra™ from Inner Balance
OestraTM is a vaginal estradiol and progesterone formulation. The route itself is capable of systemic delivery; whether blood levels are low or robust depends on dose and design. Evidence supports that vaginally administered hormones appear in blood and can act systemically.

"Vaginal = local only" is a myth built from **studies of microdose products for dryness. Those products prove you can make vaginal therapy local if you want to—but they don't prove the route can't be systemic.**

Long-term Trial: vaginal progesterone is safe and effective
The ELITE clinical trial (Early versus Late Intervention Trial with Estradiol) is the only **5-year randomized study** to test oral estradiol (1 mg/day) together with cyclical ***vaginal progesterone*** (45 mg/day) against placebo.
Key findings:
Endometrial safety: After 5 years, there was no increase in endometrial cancer in the hormone group compared with placebo.
Heart health benefits: Women taking estradiol plus vaginal progesterone showed improved cardiovascular markers—suggesting reduced heart disease risk.

Why this matters for Oestra and Inner Balance:
Oestra uses the vaginal route similar to the ELITE trial. The cardiovascular improvements in ELITE further suggest that the combination of estradiol and vaginal progesterone can have whole-body advantages beyond symptom relief.

*illustrative-purposes only

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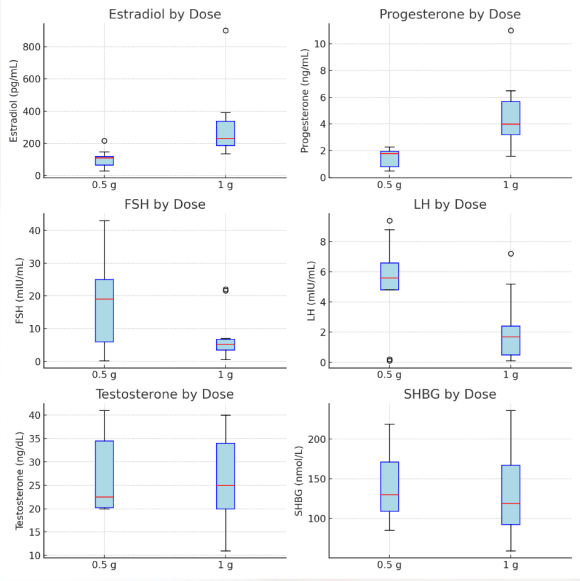
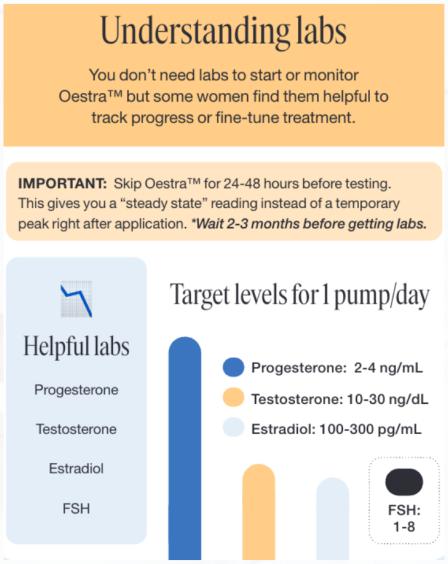
What Does Data on Oestra™ Show?

Women supplementing with Oestra daily show peak blood levels (10-12 hours) after application and steady state blood levels higher than patch & topicals. ***Data shown is steady-state measurements (24 after stopping cream).***

- ✓ **Estradiol & Progesterone:** Both hormones show higher median and overall ranges with 1 g dosing compared to 0.5 g, confirming a dose-dependent increase in blood levels (i.e. consistent with systemic absorption).
- ✓ **FSH & LH:** Levels are generally lower with 1 g dosing, consistent with stronger estrogen/progesterone feedback on the pituitary (systemic).
- ✓ **Testosterone & SHBG**: Confirms progesterone converts to testosterone. Variability is wide, which suggests individual differences in conversion to testosterone and sex hormone binding protein response.

Blood Levels at 6 months of Oestra™ Shows Systemic Circulation





Women Report Whole Body Symptom Relief on Oestra™

- **Heavy & Painful Menstrual Bleeding: 96%**
- **Sex Drive & Arousal: 75.3%**
- **Vaginal Dryness: 97%**
- **Mental Health: 78.7%**
- **Sleep: 80.2%**
- **Skin & Hair Appearance: 69.7%**
- **Weight Loss: 23.5%**
- **Energy Levels: 63%**
- **Brain Fog: 67.6%**
- **Body Aches & Pains: 58.8%**

Vaginal delivery is a route, not a dose. Low doses make it "local." Systemic-purpose doses/formulations make it systemic. If you're considering Oestra™, know that the vaginal route can be used intentionally to achieve whole-body effects with estradiol and progesterone—backed by pharmacology, real-world products, and published studies.

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Packaging label: https://www.fda.gov/drugsatfda. Crinone® 4% and Crinone® 8%

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