INFORMATIONAL; PREPARED BY INNER BALANCE FOR PROVIDERS

Clinical reference: vaginal systemic hormone delivery *and* endometrial monitoring

Purpose

This reference addresses two questions that come up frequently when patients discuss vaginally-delivered, systemic-purpose hormone therapy (Oestra®) with their broader care team: (1) whether vaginal delivery can achieve systemic effect, and (2) how to interpret endometrial thickness findings in patients on this therapy. It is intended as background, not a directive — clinical judgment for the individual patient always governs.

For context: Oestra was developed by Dr. Daccarett approximately eight years ago through direct clinical practice and has been iteratively refined since; Inner Balance was founded in 2023 and has since treated over 60,000 women. We raise this only as context, not as a substitute for dedicated pharmacokinetic and safety research. Most FDA Phase 3 trials run well under two years with far less patients, but we recognize that real-world clinical experience, however extensive, is not equivalent to a controlled trial, and we don't present it as such.

1 Vaginal delivery can be systemic — dose and formulation determine this, not route

The vaginal epithelium is highly vascularized and drains via the uterine and vaginal venous plexuses directly into systemic circulation, bypassing first-pass hepatic metabolism. This is a well-established pharmacologic principle, not specific to any one product.

RELEVANT LITERATURE

Contraceptive vaginal rings (e.g., etonogestrel/ethinyl estradiol) reliably suppress ovulation via sustained systemic hormone levels — direct clinical proof that the vaginal route can maintain systemic drug concentrations at scale.

Cicinelli et al. described the "first uterine pass effect," in which vaginally administered progesterone preferentially reaches the uterus while systemic exposure also occurs — the two are not mutually exclusive. (*Fertil Steril*, 2000)

Systematic and pharmacokinetic reviews of vaginal progesterone and estradiol confirm dose-dependent systemic absorption. (Santen et al., *Menopause*, 2020; Wu et al., *Front Pharmacol*, 2017)

IMPORTANT INTERPRETIVE NOTE

Much of the literature describing vaginal estrogen as "minimally systemic" studied low-dose products (e.g., 10–25**mcg** estradiol tablets) formulated specifically for local genitourinary symptom relief. Those findings reflect the dose studied, not a limitation of the vaginal route itself. They should not be read as establishing that vaginal delivery cannot be systemic at other doses or formulations — nor, conversely, should any single product's data be assumed to transfer to another without product-specific evidence. We do not have a dedicated pharmacokinetic study isolating Oestra's absorption percentage and do not claim a specific figure.

2 Endometrial thickness in patients on combined hormone therapy

There is no clinical indication for endometrial imaging in an asymptomatic patient

The most important point for this section is upstream of any thickness threshold: **being on hormone therapy is not, by itself, an indication for endometrial ultrasound.** The clinical indication for imaging is bleeding — not treatment status, and not a product's route of administration. An asymptomatic patient with no abnormal bleeding does not need endometrial surveillance simply because she is on Oestra, in the same way an asymptomatic patient on any FDA-approved combined HRT regimen does not need routine endometrial ultrasound absent bleeding. Ordering imaging in the absence of a bleeding indication introduces incidental findings that then require interpretation they wouldn't otherwise need — which is the scenario this section exists to address, but the better first step is not creating it.

If thickness is measured incidentally, the 4mm bleeding-triage cutoff does not apply

If an endometrial thickness measurement does exist for a given patient — incidentally, or from imaging ordered for an unrelated reason — the widely cited "4mm" threshold should not be applied to interpret it. That threshold originates from ACOG guidance on evaluating **new-onset postmenopausal bleeding** in women *not* expected to have a proliferative endometrium — it was validated as a triage tool in that specific symptomatic context, not as a reference range for asymptomatic women on hormone therapy.

The evidence base for an appropriate endometrial thickness threshold specifically in MHT users is comparatively limited. One review notes plainly that "in MHT users the ideal cut-off for invasive procedures has not been investigated thoroughly, and the evidence base for another endometrial thickness cut-off threshold is lacking." Where this has been studied directly:

Levine et al. (1995) evaluated endometrial thickness in 62 asymptomatic postmenopausal women across three hormone regimens and proposed **<8mm** as a threshold not warranting further workup in asymptomatic MHT users.

Mossa and colleagues similarly proposed an 8mm threshold, finding that a higher incidence of thickened endometrium or spotting in MHT users did not correlate with a higher incidence of malignant pathology.

An incidental endometrial thickness in the 5–10mm range in an **asymptomatic** patient on combined estrogen/progesterone therapy, with no abnormal bleeding, does not on its own warrant biopsy.

The operative rule: bleeding is the trigger, not thickness, and not treatment status

We want to be direct about this rather than soften it: ACOG's most recent guidance (April 2026) moved *away* from relying on endometrial thickness thresholds even in **symptomatic bleeding evaluation**, citing evidence that a 4mm cutoff may miss a clinically meaningful proportion of cancers. That update reinforces, rather than contradicts, the point above: thickness measurements — in a patient who has them — should not be over-relied upon in either direction, whether to reassure or to alarm.

THE STANDARD WE FOLLOW, AND RECOMMEND

Endometrial imaging is not indicated for an asymptomatic patient regardless of hormone regimen. Any bleeding pattern outside what's expected for the individual patient — prolonged, heavy, or a new change from baseline — warrants referral for in-person gynecologic evaluation, which may include ultrasound and/or biopsy per the clinician's judgment. This is the same standard applied to any patient on any hormone therapy, compounded or FDA-approved. We do not claim Oestra prevents endometrial hyperplasia or cancer, and we do not offer thickness or absorption data as a substitute for this standard.

Summary for referring providers

1. Vaginal delivery can be systemic; whether it is depends on dose and formulation, not the route.
2. Hormone therapy status alone is not an indication for routine endometrial imaging — the indication is bleeding.
3. If thickness is measured incidentally, the 4mm bleeding-triage threshold does not apply to asymptomatic MHT users; 5–10mm without bleeding does not, by itself, warrant biopsy.
4. Abnormal bleeding — not thickness, not hormone treatment status — remains the trigger for further evaluation, in this population as in any other.

We welcome direct clinical correspondence from referring or consulting providers with specific patient questions.

References available on request.