Dosing considerations for switching between routes of administration - Estradiol and Progesterone

We can use published literature data on pharmacokinetic parameters such as bioavailability to help guide our approximate starting dose selection.

Estradiol PK parameters for different routes are listed in the table below.

Route	Estradiol Dose (mg)	Peak E2 (pg/mL)	E2:E1 Ratio	Bioavailability	Advantages	Disadvantages
Oral	1–2	25–80	1:5	Low (≈5%)	Convenient, widely used	High hepatic first-pass metabolism; high estrone levels
Transdermal (Patch)	25 to 100 µg/day	40–80	1:1	Moderate (≈20%)	Avoids first-pass; steady delivery	Skin irritation, adhesion issues
Transdermal (Gel)	1.5 mg	60–120	1:1	~10–15%	Flexible dosing	Variability with application site
Sublingual	0.25–1	300–450	1:3	~50%	Fast onset; avoids first-pass	Bitter taste possible
Buccal	0.25	500	–	High	Convenient, avoids first-pass	Bitter taste possible
Intranasal	300 µg	~800–1000	2:1	Moderate	Pulsatile delivery; rapid onset	Nasal irritation, sneezing
Vaginal (Cream)	0.2–2	80–530	1:5	High	High absorption, local effect	Variable systemic effect
Vaginal (Ring)	50–200 µg/day	40–150	~1:2–1:5	High	Sustained release	Expulsion risk
Intramuscular	–	–	1:2	Nearly 100%	Long-lasting levels	Pain, depot effect
Subcutaneous (Implant)	–	–	1:1.5	High	Long-term release	Invasive

Note: E2 = Estradiol, E1 = Estrone

Progesterone PK parameters for different routes are listed in the table below.

Route	Compound	Dose (mg)	Cmax (ng/mL)	Tmax (h)	Bioavailability	Advantages	Disadvantages
Oral	Micronized Progesterone	100–200	2–12	1–4	Very low (~5–10%)	Convenient, effective for endometrial protection	Extensive metabolism, sedation, low systemic P4
Vaginal	Micronized Progesterone	100–400	5–16	5–6	High (local + systemic)	Uterine targeting (first-uterine pass), sustained levels	Some local irritation or leakage
Intramuscular	Progesterone in oil	100	40–80	8	~100%	High sustained serum levels, effective luteal support	Pain, invasive, depot persistence
Buccal	Progesterone	100	~8	1.3	Moderate (~50%)	Non-invasive, avoids hepatic metabolism	bitter taste
Intranasal	Progesterone	11.2 × 3/day	3.75 → 6.0	~1–4	18% (up to 58% with cyclodextrin)	Pulsatile, rapid onset, convenient	Needs frequent dosing, nasal irritation
Transdermal	Progesterone cream	20–40	0.1–1.0	–	Poor (<10%)	Non-invasive, good for vasomotor symptom relief	Low systemic levels, variable absorption

Key Benefits of Buccal and Sublingual "V" strips for Estradiol and Progesterone:

Parameter	Buccal/Sublingual Estradiol	Buccal Progesterone
1. Avoidance of First-Pass Effect	Bypasses hepatic first-pass metabolism → ↓SHBG, ↓estrone formation → maintains physiological E2:E1 ratio	Avoids hepatic metabolism → more predictable P4 levels
2. High Bioavailability	~50–70% (vs. ~5% oral) → requires lower doses for efficacy	~50% (vs. ~10% oral) → greater endometrial protection
3. Rapid Onset of Action	Peak levels in 20–30 min → useful for rapid symptom relief (e.g., hot flushes, mood swings)	Effective luteal support in fertility therapy or HRT
4. More Physiological Hormone Profile	Sublingual route maintains **higher estradiol** and **lower estrone** levels → mimics premenopausal patterns better	Delivers P4 without overshooting synthetic progestin levels
5. Dose Flexibility	Easy titration of low doses (e.g., 0.25–1 mg)	Can be combined with estradiol in compounded formulations
6. Fewer Metabolite-Driven Side Effects	Less conversion to estrone sulfate and estrogen conjugates → ↓risk of nausea, breast tenderness	Reduced central nervous sedation vs oral P4
7. Alternative for Patients Intolerant to Other Routes	Ideal for women with poor GI tolerance (oral), skin issues (transdermal), or vaginal discomfort	Useful where vaginal route is not tolerated or contraindicated
8. Clinical Indications	- Menopausal HRT (vasomotor symptoms) - Acute symptom control - Early menopause	- Endometrial protection in HRT - Luteal phase support in ART
9. Reduction of Hepatic Effects	↓ impact on liver protein synthesis (e.g., SHBG, angiotensinogen) → favorable lipid and clotting profile	Reduces risk of increased clotting factors associated with oral use

Supporting Clinical Insights:

- E**stradiol (sublingual)** has been shown to produce **300–450 pg/mL** serum levels within 30 minutes—far superior to oral estradiol at the same dose, and with a **more favorable estradiol:estrone ratio (1:3 vs. 1:5 orally)**.
- **Buccal progesterone** (e.g., 50/100 mg) leads to peak P4 levels of ~8 ng/mL, **adequate for endometrial protection**, and avoids the excessive hepatic metabolism seen with oral dosing.
- Both routes support **pulsatile or flexible regimens**, which may benefit **younger women with premature ovarian insufficiency (POI)** or **patients requiring dynamic hormonal therapy**, such as those with hormone-sensitive mood disorders.

Reference:

Pharmacology of estrogens and progestogens: influence of different routes of administration; Climacteric. 2005 Aug:8 Suppl 1:3-63.

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