Estrone and Estradiol Are Not One Number: The Clinical Value of Measuring Both Estrogens — and Their Ratio

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ABSTRACT

Rationale. In routine practice, "estrogen status" is frequently reduced to a single estradiol measurement, often by immunoassay. Yet estrone (E1) and estradiol (E2) are distinct, interconverting estrogens that differ in potency, tissue source, and clinical meaning, and a single value cannot represent both.

Key distinctions. E2 is the potent, high-affinity estrogen and predominates premenopausally; E1 is a weaker estrogen (~1/3–1/10 of E2's potency) that predominates after menopause through peripheral aromatization. The two interconvert via 17β-hydroxysteroid dehydrogenase (17β-HSD), with estrone sulfate serving as a large circulating reservoir. Consequently the E2:E1 ratio is not fixed — it inverts across the menopausal transition and shifts with the route of estrogen therapy.

Clinical implications. Measuring both estrogens and reading their ratio informs menopausal status, the route and adequacy of hormone therapy, ovarian function recovery during aromatase-inhibitor treatment, aromatization, and estrogen-related cancer risk — provided the assay is sensitive enough to be trusted at low concentrations.

Conclusion. A single estrogen is an incomplete readout. Paired E1/E2 measurement, interpreted through the ratio, yields information neither analyte provides alone.

Keywords: estradiol · estrone · E2:E1 ratio · aromatase (CYP19A1) · 17β-HSD · estrone sulfate · menopause · hormone therapy · LC–MS/MS

1 Background

Estrone (E1) and estradiol (E2) are the two principal circulating estrogens in humans. Conventional "estrogen" testing reports estradiol alone — historically by immunoassay — which quietly equates one estrogen with total estrogen status. That equivalence does not hold: E1 and E2 differ in potency and origin, they interconvert, and the balance between them changes with reproductive stage and with how estrogen is administered. This review sets out the biochemical and clinical case for measuring both estrogens and interpreting their ratio, and for doing so with an assay sensitive enough to be reliable at the low concentrations that matter most.

2 Two estrogens, one interconverting pool

Aromatase (CYP19A1) converts androstenedione to estrone and testosterone to estradiol. The two estrogens are then interconverted by 17β-hydroxysteroid dehydrogenase (17β-HSD): reduction favors E2, oxidation favors E1. Estrone is additionally stored as estrone sulfate (E1S) — the most abundant

circulating estrogen — through the opposing actions of sulfotransferase (SULT1E1) and steroid sulfatase (STS), forming a deep reservoir that can regenerate active estrogen.[12] Functionally, E2 is the potent, high-affinity ligand for estrogen receptors ERα and ERβ, whereas E1 is a comparatively weak estrogen that behaves as a convertible reservoir (Figure 2). The clinical corollary: E2 reports potent estrogenic drive, while E1 reports the peripheral, reservoir arm of estrogen supply.

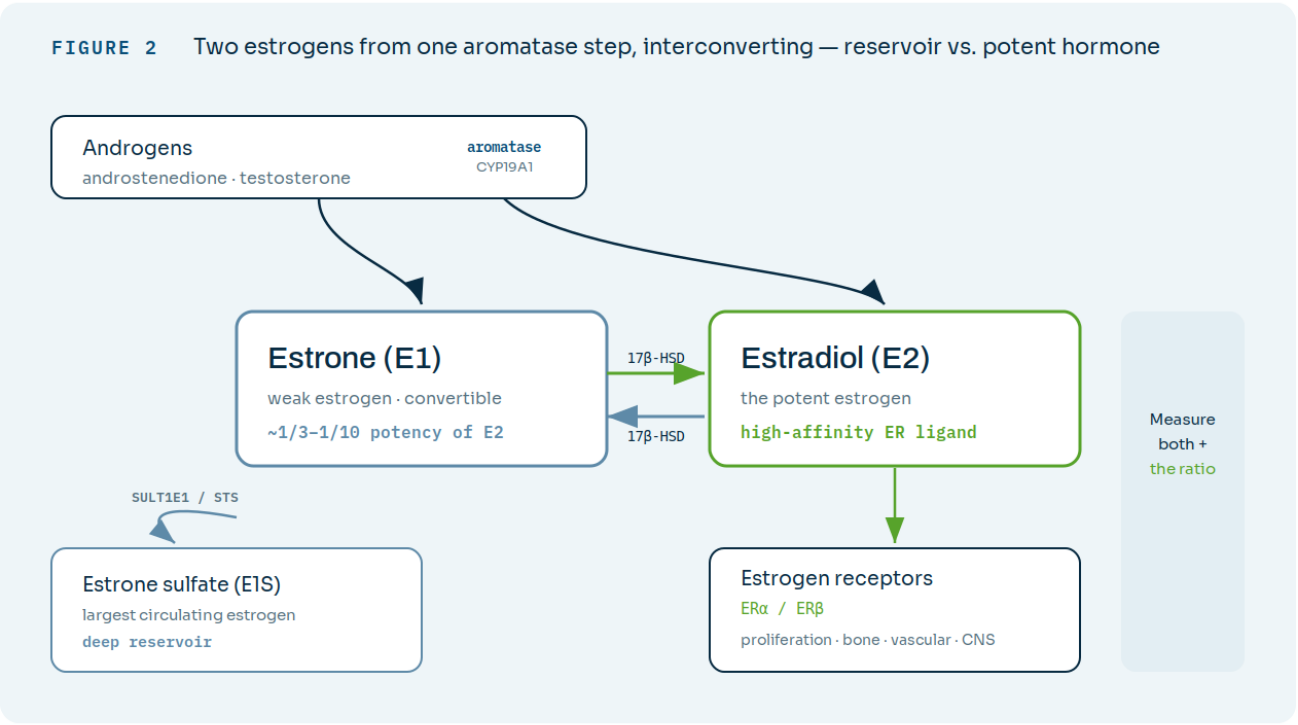

Figure 2. Estrogen synthesis and interconversion. Aromatase (CYP19A1) generates E1 and E2 from androgen precursors; 17β-HSD interconverts them; estrone sulfate is a large circulating reservoir. Only E2 is a high-affinity ER ligand, so the two analytes report different arms of estrogen physiology.

3 The ratio inverts across the menopausal transition

Before menopause, ovarian granulosa cells secrete estradiol as the dominant estrogen, and E2 exceeds E1. After menopause, ovarian estradiol output falls and the dominant source becomes peripheral aromatization of androgens in adipose and other tissues — which yields estrone. As a result the balance inverts, and E1 becomes the dominant circulating estrogen. Ultrasensitive LC–MS/MS reference ranges illustrate the postmenopausal pattern directly: estradiol on the order of 3.8–36 pmol/L against estrone of roughly 22–122 pmol/L.[3] A panel reporting a single estrogen cannot represent this stage-dependent shift; the ratio makes it explicit (Figure 1).

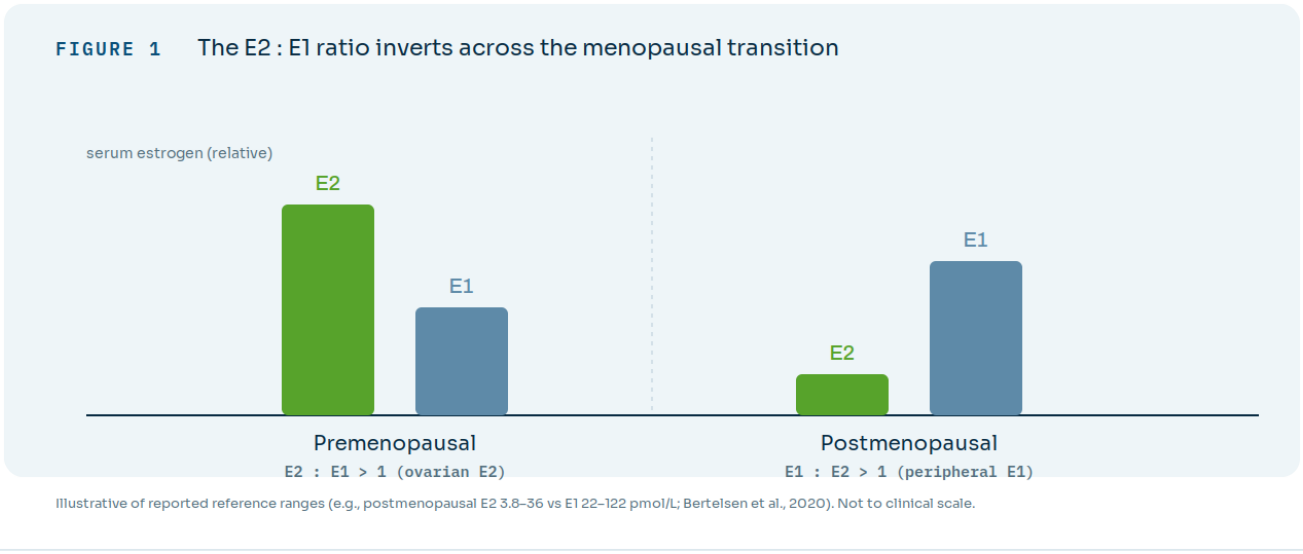

Figure 1. The E2:E1 ratio inverts at menopause. Premenopausally, ovarian estradiol dominates (E2 > E1); postmenopausally, peripheral aromatization makes estrone dominant (E1 > E2). Illustrative of reported reference ranges;[3] not to clinical scale.

4 The ratio shifts with the route of estrogen therapy

The E2:E1 ratio also reports how estrogen is delivered. Oral estradiol undergoes extensive first-pass hepatic metabolism, a substantial fraction of it converted to estrone, which lowers the circulating E2:E1 ratio. Non-oral routes preserve a more physiologic ratio. A direct pharmacokinetic comparison found a higher E2-to-E1 ratio with sublingual than with oral 17β-estradiol (approximately 1.1 vs 0.7),[4] and oral administration raises estrone and its metabolites relative to transdermal delivery.[5] Because the ratio encodes the route, it can corroborate the prescribed preparation, flag non-adherence, and inform whether a physiologic estrogen profile is being achieved in menopausal hormone therapy or gender-affirming therapy.

5 Applications favoring measurement of both estrogens

5.1 Menopausal status and estrogen-therapy monitoring

The E2:E1 ratio helps confirm menopausal transition and reflects the route of administration, supporting individualized adjustment of hormone therapy.[34] A single estrogen value cannot distinguish an estrone-dominant postmenopausal profile from an oral-therapy profile; the pair can.

5.2 Ovarian function recovery during aromatase-inhibitor therapy

In younger women treated with an aromatase inhibitor, undetected ovarian reactivation compromises treatment. Estrone may be the more sensitive marker of ovarian function recovery, and reliable detection at the very low concentrations produced during estrogen suppression requires an ultrasensitive assay measuring both estrogens.[63]

5.3 Estrogen-related cancer risk context

In postmenopausal women, higher estradiol and estrone — including the estrone-sulfate reservoir — are associated with breast-cancer risk in pooled and umbrella analyses.[78] Characterizing both estrogens supports a more complete picture than estradiol alone.

5.4 Aromatization and estrogen in men

Estrogens circulate at low but physiologically meaningful concentrations in men, generated by aromatization, where estradiol contributes to bone, vascular, and metabolic physiology. Quantifying both estrogens characterizes aromatization status in ranges where immunoassay is unreliable.[9]

6 Analytical considerations

The concentrations that matter most clinically are low. Estrogens commonly fall below 20 pg/mL in postmenopausal women and in men, and far lower under aromatase-inhibitor therapy — ranges in which conventional immunoassays lack the specificity and accuracy to be trusted.[19] Validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) achieves sub-picogram-per-milliliter limits of quantitation, meets the Endocrine Society's stated requirements for estradiol measurement, and quantifies estrone concurrently in the same run.[3] Laboratories able to report accurate, simultaneous estradiol and estrone by LC–MS/MS therefore provide information that single-estrogen immunoassays cannot.

Table 1. Estradiol (E2) versus estrone (E1) at a glance.

Property	Estradiol (E2)	Estrone (E1)
Biological role	Potent estrogen; high-affinity ER ligand	Weak estrogen (~1/3–1/10); convertible reservoir
Predominates in	Premenopause (ovarian)	Postmenopause (peripheral aromatization)
Principal source	Ovarian granulosa; aromatization of testosterone	Aromatization of androstenedione; adipose tissue
Interconversion	⇌ E1 via 17β-HSD	⇌ E2 via 17β-HSD; estrone-sulfate reservoir
Effect of oral estrogen	Raised less (first-pass lowers E2:E1)	Raised markedly (first-pass conversion)
Preferred assay	LC–MS/MS (immunoassay unreliable at low levels)	LC–MS/MS
Distinct utility	Potent-estrogen drive; AI suppression	Menopausal / route status; ovarian recovery; reservoir

7 Conclusions and recommendations

A single estradiol value should not be equated with estrogen status. Measure estrone and estradiol together, and read the ratio: it separates premenopausal from postmenopausal physiology, reveals the route of estrogen therapy, and adds aromatization and risk context that one analyte cannot. Most importantly, interpret the two as a pair — and use an assay sensitive enough to be trusted at the low concentrations where these questions are actually decided.

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