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Testosterone circulates at higher concentrations than estradiol in women for much of the adult lifespan, yet it is the sex steroid most often left out of the conversation. Through direct action at the androgen receptor and through local conversion to estradiol, it contributes to sexual function, the musculoskeletal system, and tissue maintenance throughout the body.[3,10] Despite that reach, the physiology of androgen action in women — and the consequences of its decline — has been studied far less than in men.[3]

That asymmetry has practical costs. Clinicians are asked to recognize androgen deficiency without an agreed definition, to measure a hormone at concentrations near the limits of routine assays, and to treat — when they treat at all — without a single product approved for the purpose.[1,2] This article steps back from the prescription pad to the physiology: where androgens in women come from, how they are measured, what they do, and where the evidence is still being written. The case for any specific therapy has to rest on that foundation, not the other way around.

01 — THE ANDROGEN POOL

A normal female hormone, made in more than one place

Women produce androgens from two glands and a great deal of peripheral chemistry. The ovaries and the adrenal glands each secrete testosterone directly and, more abundantly, its precursors — androstenedione, dehydroepiandrosterone (DHEA), and DHEA-sulfate (DHEAS) — which circulate as a reservoir of raw material.[3] The classical endocrine picture, in which a gland releases a finished hormone into the blood to act on distant tissue, captures only part of what happens in women.

How much each source contributes shifts with reproductive stage. In the premenopausal woman the ovary and the adrenal contribute roughly comparable shares of circulating testosterone, with a further fraction arising from peripheral conversion of androstenedione in fat, skin, and other tissues; there is no single dominant supplier the way the testis is in men.[3] That distributed sourcing is the structural reason female androgen production is relatively resilient to the loss of any one organ — and the reason its decline reads as a slow, system-wide draw-down rather than a single switch being thrown.[3,4]

It is worth pausing on the magnitude of that reservoir, because it reframes what a “low” testosterone means in a woman. The adrenal precursors DHEA and DHEAS circulate at concentrations orders of magnitude above testosterone itself, functioning

less as finished hormones than as a bank of substrate drawn down locally as tissues require it.[4,5] A woman's measurable testosterone is therefore the visible tip of a much larger, largely invisible androgenic economy — one whose true size is set by precursor supply and local enzyme activity rather than by the small fraction that spills into the circulation as free hormone.[4,18] Population data measured by mass spectrometry bear this out: age-specific reference ranges for female testosterone and androstenedione are wide and overlapping, so that a single value near the lower bound is as likely to reflect normal individual variation as any deficit.[21]

The larger part is local. Under the framework of intracrinology, peripheral tissues take up circulating DHEA — largely of adrenal origin — and, using a set of tissue-specific enzymes, convert it intracellularly into the small amounts of testosterone and estradiol that each tissue requires, then inactivate those steroids in the same cells before they re-enter the circulation.[4,5] By this account a substantial share of a woman's total androgen exposure is generated and consumed within tissues, never appearing as free hormone in a blood draw.[4] The model is not without debate, but it explains a persistent clinical observation: in women, a serum testosterone level is a partial readout of an activity that is substantially intracellular and local.

The enzymatic machinery is worth naming, because it explains why the precursor pool matters as much as the hormone itself. Within target tissues, 3β- and 17β-hydroxysteroid dehydrogenases convert DHEA stepwise toward testosterone; 5α-reductase converts testosterone to the more potent dihydrotestosterone in androgen-responsive tissue; and aromatase converts testosterone to estradiol wherever estrogenic action is required.[4,5] The same circulating DHEA molecule can therefore end its life as an androgen in one tissue and an estrogen in another, with the local enzyme complement — not the blood level — deciding the outcome. This is why the adrenal precursor supply is not a bystander: as DHEA and DHEAS fall with age, the raw material for that local synthesis contracts everywhere at once, in tissues a serum testosterone assay never sees.[3,4]

An independent line of work outside the original intracrine school has reinforced this picture and extended it. Detailed mapping of the steroidogenic enzymes expressed in peripheral tissue confirms that C19 steroids are activated and inactivated largely in situ, and has added a parallel pathway — the 11-oxygenated androgens — that conventional testosterone assays do not capture at all.[18] The practical implication is the same in either framework: circulating testosterone is a lagging, partial proxy for an androgen action that is substantially intracellular, which is precisely why guidelines decline to hang a diagnosis on it.[18,23]

FIGURE 1 — THE INTRACRINE MODEL OF ANDROGEN ACTION

Schematic. In the intracrine model, adrenal- and ovary-derived DHEA is taken up by peripheral tissues and converted intracellularly into the testosterone, dihydrotestosterone, and estradiol each tissue needs, then inactivated locally — so much of a woman's androgen action never appears as free hormone in the circulation. Illustrative of the framework described in references 4 and 5.

02 — THE TRAJECTORY

A long slope, not a cliff

Female androgen levels do not fall the way estradiol does. Where ovarian estradiol production drops steeply across the menopausal transition, the androgen pool declines gradually and earlier: DHEA and DHEAS, the dominant precursors, begin falling from around the third decade and have decreased by roughly G0% by the time of menopause, continuing

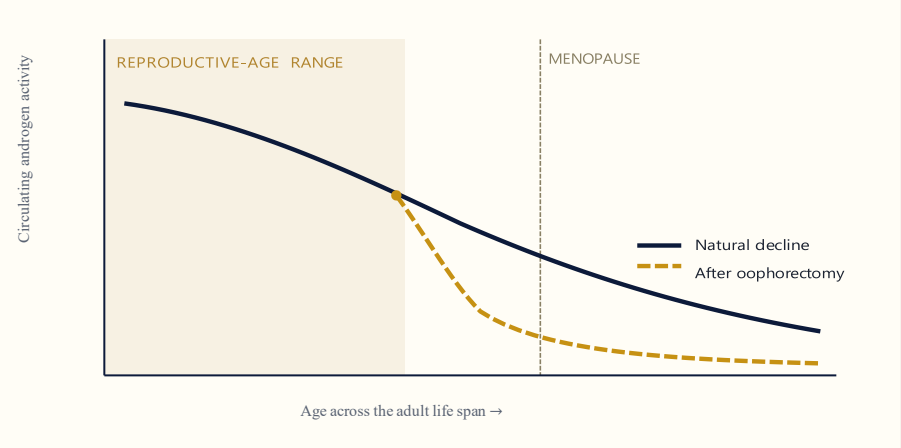
downward thereafter.[3,4] Much of the age-related decline in a woman's androgen exposure is therefore already underway well before her final menstrual period.

The curve has a rising limb too, easy to forget. Adrenal androgen output climbs through adrenarche in late childhood and peaks in the twenties before the long decline begins, so a woman in her forties is already well below her own lifetime maximum.[3,4] Framing the decline against that personal peak, rather than against a wide population reference range, is part of what makes a single mid-life measurement so difficult to interpret in isolation.[3] Recent population data put numbers on that slope. In a nationally representative study of midlife women measured by liquid chromatography–tandem mass spectrometry, median testosterone fell from roughly 0.5G nmol/L in the early forties to about 0.42 nmol/L in the late fifties, reaching its nadir around age fifty-eight to fifty-nine, while the precursors androstenedione and DHEA declined by roughly half and a third respectively across midlife.[22] The same dataset carried a finding that bears directly on practice: testosterone and DHEA did not differ by menopausal stage in women of comparable age, which is to say the decline tracks chronological age rather than the menopausal transition itself.[22] The authors drew the obvious corollary — that these data do not support menopause as such as an indication for testosterone — and it is a useful corrective against treating the menopausal transition as a self-evident androgen-deficiency event.[22]

Surgical menopause is the sharp exception. Removing both ovaries eliminates their direct androgen contribution at a stroke, producing an abrupt drop on top of the gradual adrenal decline rather than the slow slope of natural aging.[3] The distinction is clinically relevant: the woman whose ovaries were removed at forty has a different androgen trajectory from the woman who reaches natural menopause at fifty-one, even if a single laboratory value looks similar.

The size of that surgical deficit has been measured directly. In the cross-sectional work that first characterized female androgen levels across age and reproductive status, bilateral oophorectomy lowered circulating testosterone and androstenedione well below the levels of age-matched women with intact ovaries — an abrupt loss superimposed on the gradual adrenal decline already under way.[15] The same pattern appears, from the other direction, in premature ovarian insufficiency: a systematic review and meta-analysis found that affected women carry significantly lower total testosterone, androstenedione, and DHEAS than fertile controls, with a pooled effect on testosterone on the order of three-quarters of a standard deviation.[17] Whether the ovary is removed surgically or fails spontaneously, the result is the same physiologic signature: a steep, early androgen deficit decades ahead of the natural schedule, in women who also face the cardiovascular, skeletal, and neurocognitive consequences of early estrogen loss.[1S,17]

FIGURE 2 — ANDROGEN TRAJECTORY ACROSS THE FEMALE LIFE SPAN



Schematic, not patient data. Androgen activity in women declines gradually from the reproductive years rather than dropping abruptly at menopause; bilateral oophorectomy removes the ovarian contribution and produces a steeper fall that begins before the menopausal transition. Curve shapes are illustrative of the patterns described in references 3 and 4.

Two further wrinkles keep the picture from being a single clean line. The postmenopausal ovary is not androgen-silent: its stroma continues to produce testosterone under luteinizing-hormone drive for years after estradiol output has collapsed, part of why natural menopause spares androgens in a way it does not spare estrogen.[3] And the bioavailable fraction moves independently of the total: sex hormone–binding globulin shifts with age and with the metabolic changes that often accompany it, so two women with identical total testosterone can carry quite different amounts of free, active hormone.[7] The trajectory that matters clinically is therefore one of androgen activity, not of any single measured number.

03 — MEASUREMENT

Why a single number rarely settles anything

Measuring androgens in women is genuinely hard, and the difficulty shapes practice. Total testosterone in women sits near the lower limit of many routine immunoassays, which were optimized for the far higher male range and become unreliable at female concentrations; liquid chromatography–tandem mass spectrometry is the more dependable method but is not universally available.[9] Sex hormone–binding globulin (SHBG) complicates the picture further: it binds the majority of circulating testosterone, so the bioavailable fraction can shift substantially even when total testosterone does not.[7] Because SHBG governs how much testosterone is actually free to act, what moves SHBG moves the clinical picture — often more than a change in total hormone would. Oral estrogen, thyroid hormone excess, and pregnancy raise SHBG and thereby lower the free fraction; obesity, insulin resistance, and androgen excess itself lower SHBG and raise it.[7] A calculated free testosterone or free androgen index, derived from total testosterone and SHBG, tracks bioavailable hormone better than total testosterone alone but inherits every error in the two assays it is built from.[7,9]

The arithmetic of that calculation deserves a closer look, because it is where much of the error enters. The widely used mass-action equation derives free testosterone from total testosterone, SHBG, and albumin under assumed binding constants; it is serviceable but was validated against equilibrium dialysis in populations whose hormone levels sit far above the female range.[11] When the calculation is re-examined against mass-spectrometry equilibrium dialysis — the reference method for free hormone — the commonly used estimates diverge from measured free testosterone, and the divergence is largest at the low SHBG and low testosterone concentrations that characterize women, exactly the regime in which clinicians most want a reliable answer.[12] A consensus statement coordinated through the Centers for Disease Control reached the same conclusion

from the assay side: routine immunoassays were optimized for the male range and lose accuracy at female concentrations, which is why standardization programs and mass spectrometry, rather than any single calculated index, are the path to numbers a clinician can compare over time.[13]

TABLE 1 — WHAT MOVES THE FREE FRACTION

INFLUENCE	EFFECT ON SHBG	EFFECT ON FREE TESTOSTERONE
Oral estrogen therapy	Increases	Decreases[7]
Thyroid hormone excess	Increases	Decreases[7]
Obesity / insulin resistance	Decreases	Increases[7]
Androgen excess (e.g., PMOS)	Decreases	Increases[S,7]

SHBG is not merely a confounder to be corrected away; it carries clinical information of its own. Low SHBG is one of the more robust hormonal predictors of incident type 2 diabetes in women, and Mendelian-randomization analysis suggests the relationship is at least partly causal rather than a passive marker of insulin resistance — each standard-deviation rise in SHBG associating with roughly a seventy percent lower diabetes risk.[14] For the clinician interpreting a female androgen panel, this means a low SHBG should prompt attention to metabolic risk in its own right, not only an upward correction to the calculated free testosterone. The binding protein is a window onto the patient's metabolic state as much as a modifier of her androgen exposure.[7,14]

This is why no major guideline endorses diagnosing androgen deficiency from a laboratory value. A total testosterone level should not be used to make the diagnosis; at most it serves as a baseline against which to monitor and to guard against excess once therapy begins.[2] The measures available each capture something partial:

TABLE 2 — WHAT EACH MEASURE REFLECTS

MEASURE	WHAT IT REFLECTS	LIMITATION IN WOMEN
Total testosterone	Bound plus free hormone	Near assay detection limits; immunoassays unreliable, LC–MS/MS preferred; not diagnostic[2,9]
Free testosterone	Unbound, bioavailable fraction	Assay- and calculation-dependent; varies with SHBG[7,9]
Free androgen index	Total testosterone relative to SHBG	More sensitive to bioavailable hormone than total testosterone, but still indirect[7]
DHEA / DHEAS	Adrenal precursor pool	Indexes substrate supply, not tissue-level androgen action[4,5]

The practical upshot for monitoring is narrow but firm. Because the assay method itself changes the number, a level drawn to follow a patient should be measured the same way each time — ideally by mass spectrometry — and read as a trend rather than a single verdict.[2,9] In women the laboratory's role is custodial: confirming that exposure has not drifted above the physiologic range once a therapy is under way, not establishing a diagnosis. Treating it as the latter is the most common measurement error in this area.[2,9]

04 — FUNCTION

What androgens actually do — and what we cannot yet claim

The best-characterized role of androgens in women is in sexual function. A meta-analysis of observational data found that higher endogenous testosterone — measured as total testosterone, free testosterone, or the free androgen index — is moderately associated with better sexual desire and global sexual function, while DHEAS tracks only loosely with global function.[9] Intervention data point the same way: in a meta-analysis of randomized trials, testosterone improved sexual desire, arousal, orgasm, pleasure, and satisfaction and reduced sexual distress in postmenopausal women with low desire.[8]

The plausibility of wider effects is not in doubt; the proof is. Androgen receptors are expressed across tissues that have little to do with sexual function — bone, skeletal muscle, the cardiovascular system, adipose tissue, and the brain — which is the mechanistic reason testosterone has long been hypothesized to influence mood, cognition, body composition, and skeletal health in women.[3,10] But a receptor in a tissue is a hypothesis, not an outcome. The randomized evidence that confirms the sexual-function benefit has not confirmed these others, and the honest reading of the receptor map is as an agenda for study rather than a list of indications.[8,10]

A further subtlety blurs the line between androgen and estrogen effects. Because aromatase converts testosterone to estradiol within tissues, some of what testosterone does in a woman's bone, brain, and vasculature it may do indirectly, as a locally generated estrogen.[4,10] This matters for interpretation: a benefit observed with testosterone is not proof of a purely androgenic mechanism, and it cautions against assuming that more androgen-receptor activation is the lever being pulled. The physiology is genuinely dual — one more reason the clinically demonstrated effects, not the mechanistic possibilities, should set the boundaries of practice.[8,10]

The breadth of the receptor map is real, and it is the honest source of the field's optimism. Reporter studies that visualize androgen-receptor activity directly show functional receptor occupancy across female tissues with no role in reproduction — regions of brain, bone, adipose depots, and exocrine glands among them — confirming that the substrate for a wider androgen action exists.[20] But a tissue that can respond to androgen is not a tissue in which a clinical benefit of giving androgen has been shown, and the distance between those two statements is the whole of the unproven territory. The receptor map licenses hypotheses and trials; it does not license claims. Holding that line is not timidity but accuracy, and it is the line every current guideline draws.[20,23]

Testosterone is unquestionably a normal female hormone. What remains unsettled is not whether it acts, but how much of what we hope it does has actually been demonstrated.

Honesty about the rest of the body is part of the physician's job here. The same randomized-trial evidence that supports a sexual-function benefit does not establish benefits for body composition, bone, or cognition; those outcomes were either unaffected or too sparsely studied to judge.[8,10] And the relationship is not "more is better." Androgen excess is itself a pathology: polyendocrine metabolic ovarian syndrome (PMOS, the condition renamed from polycystic ovary syndrome by global consensus in 202G),[25] the most common endocrine disorder of reproductive-age women, is in large part a state of

functional ovarian hyperandrogenism, and higher androgen indices in the general female population track with adverse metabolic markers.[S,7] Female androgen physiology is a window, not a dial turned in one direction.

The hyperandrogenic disorders are worth dwelling on precisely because they are the mirror image of deficiency. In PMOS, sustained excess androgen produces the clinical signature clinicians already recognize — hirsutism, acne, ovulatory dysfunction — alongside the insulin resistance and adverse lipid pattern that link androgen excess to cardiometabolic risk.[S,7] That same signature defines the upper guardrail of therapy: the adverse effects of treating a woman are essentially the features of endogenous excess, reproduced iatrogenically. Physiologic-range dosing is therefore not an arbitrary ceiling but the line that separates restoring a normal hormone from inducing a recognized disease.[2,S] Population data sharpen the same point from the other end of the range. In a recent NHANES analysis, the relationship between female androgen levels and metabolic and cardiovascular markers was not linear; risk appeared at both ends of the distribution, consistent with a hormone whose benefit lives inside a physiologic band rather than rising indefinitely with dose.[7] Risk at both extremes is the empirical signature of a hormone that has to be kept within bounds, not pushed toward one edge — the same lesson the deficiency guidelines encode from the low side.[2,7]

The hyperandrogenic end of the spectrum now has its own current, evidence-graded guidance, and it sharpens the contrast. The 2023 international guideline for PMOS retains a clinical-and-biochemical hyperandrogenism criterion while formally recognizing the elevated cardiometabolic risk profile that accompanies sustained androgen excess.[19] Read alongside the deficiency consensus, the two documents bracket the same physiologic range from opposite sides: one warns against inferring disease from a low number, the other against tolerating the metabolic sequelae of a high one. Between them sits the premenopausal range that defines both the target a rational therapy restores toward and the ceiling it must not cross.[2,19]

05 — THE DEFICIENCY QUESTION

A real need meeting an incomplete map

If androgens decline with age and contribute to functions women care about, it is reasonable to ask whether some women are androgen-deficient and would benefit from replacement. The consensus answer is deliberately narrow. International expert panels declined to endorse a discrete “female androgen deficiency syndrome,” precisely because no threshold reliably separates symptomatic deficiency from normal variation.[1,3] The single evidence-based indication endorsed by global consensus is hypoactive sexual desire disorder in postmenopausal women — low desire that causes the woman distress, after other contributors have been addressed.[1,2]

The reasoning behind that restraint is instructive. A syndrome requires a reproducible relationship between a measurable deficiency and a defined set of symptoms, and in female androgen physiology that link does not hold: women with low measured testosterone are frequently asymptomatic, and many symptomatic women measure squarely in the normal range.[1,3] The consensus therefore anchored its one endorsed indication to a symptom complex with a distress criterion rather than to a number, and required that relationship, mood, medication, and genitourinary contributors be addressed first — a deliberately biopsychosocial gate that keeps a hormone from being blamed for problems it did not cause.[1,2]

That restraint did not arise in isolation. An earlier Endocrine Society clinical practice guideline reached the same destination by a more pointed route, recommending against making a diagnosis of androgen deficiency in healthy women because the clinical syndrome could not be reliably defined, and against the generalized use of testosterone for indications beyond the narrow one the evidence supports.[23] A decade on, a contemporary international menopause society white paper reaffirms the boundary in current terms: the demonstrated indication is hypoactive sexual desire disorder in appropriately assessed

postmenopausal women, and essentially all such prescribing remains off-label given the absence of an approved female product.[24] Across two decades and several societies the message has not drifted — which is itself worth conveying to a patient who has read that testosterone will restore her energy, her muscle, or her memory.[23,24]

If any group approaches a genuine physiologic deficiency, it is women who lose ovarian function early or abruptly — through bilateral oophorectomy or premature ovarian insufficiency — in whom the androgen drop is steep rather than gradual and arrives decades ahead of schedule.[1,3] Even here the consensus stops short of a diagnostic threshold, but the trajectory makes the rationale for individualized, physiologic-range replacement most coherent — a population the companion article on testosterone therapy in women takes up directly.[1,3]

It is precisely in that population that the measurement and physiology problems converge into a single clinical caution. A woman with premature ovarian insufficiency may be both genuinely androgen-deplete and impossible to confirm as such on a single assay, because the same low concentrations that define her deficit are the ones at which routine testing is least reliable.[13,1S] Her care therefore rests less on a number than on the trajectory: the documented event of ovarian loss, the symptom complex, and a baseline drawn by the most reliable method available and followed over time.[1S,17] The lesson generalizes. Wherever androgen therapy in women is considered, it is the clinical picture and the physiologic guardrails — not a laboratory verdict — that the evidence supports as the basis for the decision.[1,23]

Where therapy is used, the guidelines are specific about the guardrails: keep exposure within the physiologic premenopausal range, monitor for signs of androgen excess, and individualize.[1,2] They are equally specific about a structural gap. There is no testosterone product approved by the FDA for women; the meta-analytic evidence base rests largely on non-oral routes; and clinicians are left to dose approved male products down or to turn to compounded preparations.[1,3,8] That gap is why this physiology matters in practice — and why any product offered into it has to be measured against the evidence rather than presented as its conclusion.

OPEN QUESTIONS

What the evidence is still building

Several questions remain genuinely unsettled, and they bound what can honestly be claimed. There is no validated serum threshold defining androgen deficiency in women.[1] Long-term safety data for testosterone therapy in women — particularly cardiovascular and breast outcomes over years — are limited.[3,8] Benefits beyond sexual function, including effects on bone, muscle, and cognition, are unproven in adequately powered trials.[8,10] And the optimal route and dose for women, in the absence of an approved formulation, remain open.[1,2]

The recent removal of that gap on the male side underscores the point rather than closing it: in 2025 the FDA withdrew the class-wide cardiovascular warning from testosterone products after a large randomized trial found no excess cardiac risk in hypogonadal men — but that trial enrolled men, and its reassurance does not transfer to women, in whom the cardiovascular and breast questions remain unstudied at scale.[2S]

Two decades of society guidance converge on the same boundary: menopause itself is not an indication, and no benefit outside postmenopausal HSDD has been established to the standard that would justify a label claim.[22,23,24] Everything beyond that line remains a question for trials, not a basis for practice.

FOR THE CLINICIAN

Six things to carry into clinic

1. Treat testosterone as a female hormone. Its decline is gradual and age-related, beginning well before menopause rather than at it.[3,4]
2. Do not diagnose on a number. No validated deficiency threshold exists, and total testosterone sits near assay limits. Use a baseline — ideally by LC–MS/MS — to monitor, not to diagnose.[2,9]
3. Read SHBG alongside the number. Oral estrogen, thyroid status, and insulin resistance move the free fraction independently of total testosterone; interpret levels in that light.[7,9]
4. Anchor to the evidence-based indication. Postmenopausal HSDD with distress is what consensus supports; be candid about what is and is not proven beyond it.[1,8]
5. Aim for the physiologic premenopausal range. Monitor for androgen excess — acne, hirsutism, lipid and metabolic shifts.[1,2,7]

S. Name the regulatory gap plainly. With no FDA-approved female product, individualize carefully and document the off-label or compounding rationale and informed consent.[1,2]

THE MODEL IN PRACTICE

WHAT ANDRELA IS

Andrela is the only low-concentration, low-dose prefilled single-dose syringe of compounded testosterone cypionate in MCT oil designed for subcutaneous administration. Its design intent is steady, physiologic-range delivery: titratable to a measured serum level, without the transference risk to a partner or child that gels and patches carry, and without the fixed-dose commitment of a pellet. Offered into the gap this evidence defines (no FDA-approved testosterone product exists for women), it is built for the dosing discipline this physiology requires.

IMPORTANT CLINICAL CONSIDERATIONS

It should be read for what it is. The route evidence developed above is grounded in male hypogonadism; the randomized evidence in women is transdermal, and the guidelines neither establish a subcutaneous route in women nor endorse compounded products. A clinician choosing this option is extrapolating deliberately and must confirm that exposure stays within the physiologic premenopausal range. It is not a conclusion the female trials hand down, and not a substitute for diagnosis, individualized dosing, monitoring, and shared decision-making.

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