Kisspeptin-10

A Clinical Learning Guide for Medical Providers

Metastin 45–54 • KISS1R / GPR54 Agonist • Hormonal & Sexual Health (1 of 3)

Evidence base at a glance: The first of three peptides in the Hormonal & Sexual Health group, and the "upstream gatekeeper" of the entire reproductive axis. Three facts dominate: (1) it works UPSTREAM of GnRH — stimulating the body's own GnRH neurons rather than supplying hormone — so the response is physiological, self-limiting, and PRESERVES the HPG feedback loop (a key advantage over exogenous testosterone or GnRH); (2) its human evidence is genuinely strong for one thing — raising LH/testosterone in men via IV — with a striking sexual DIMORPHISM in women (response depends on menstrual phase); and (3) the gap between that evidence and real-world use is large — the trials are IV, the ~4-minute half-life is very short, and whether the empirical 100–200 µg SC dose meaningfully crosses into the brain (KP-10's BBB penetration is limited, unlike KP-54) is UNPROVEN. NOT FDA-approved; WADA-prohibited since 2024.

1. Peptide Profile

Name: Kisspeptin-10 (Metastin 45–54)

Classification: KISS1R (GPR54) agonist; upstream gatekeeper of the hypothalamic–pituitary–gonadal (HPG) axis; potent GnRH stimulator

Structure: Decapeptide — 10 amino acids (YNWNSFGLRF-NH_2); ~1,302 Da. The smallest bioactive kisspeptin fragment, derived from kisspeptin-54

Gene / Receptor: Gene KISS1 (chr 1q32); receptor KISS1R / GPR54, a Gαq/11-coupled GPCR

Binding & half-life: KISS1R binding affinity equal to KP-54 (Kd ~0.03 nM); in vivo half-life ~4 min IV (~55 sec in vitro) — very short

Routes: IV bolus/infusion (clinical trials); SC (empirical clinical practice); intranasal (research, mostly KP-54)

Regulatory status: NOT FDA-approved — investigational only; WADA Prohibited List (S2: peptide hormones) since 2024

Where It Sits in the Hormonal & Sexual Health Group

This is the first of three peptides in the Hormonal & Sexual Health category. Kisspeptin-10 is the logical starting point because it acts at the very TOP of the reproductive cascade: it is the switch that tells GnRH neurons to fire. Everything downstream — GnRH → pituitary LH/FSH → gonadal testosterone/estradiol — follows from that single upstream signal. Understanding kisspeptin first therefore frames how the rest of the hormonal axis is regulated, and why an upstream, feedback-preserving approach differs fundamentally from giving exogenous hormone.

KP-10 vs KP-54: A Practical Distinction

Kisspeptin-10 is the 10-amino-acid C-terminal fragment of kisspeptin-54; both bind KISS1R with similar affinity, but they behave differently in the body. KP-54 has a longer half-life (~27.6 min vs

~4 min) and crosses the blood–brain barrier, and it is the form used as an IVF oocyte-maturation trigger. KP-10 is shorter-acting with limited BBB penetration and is used (empirically) more for sustaining pulsatile LH/FSH stimulation. A key caution for reading the literature: much of the strongest reproductive-therapeutic data — especially IVF triggering — is KP-54 data and cannot simply be assumed to apply to KP-10.

2. Modes of Action & Mechanisms

Kisspeptin-10 binds KISS1R (GPR54) on GnRH neurons and triggers a Gq/11-based signaling cascade that drives GnRH gene expression and neuronal firing. Its defining feature is position: it acts one step ABOVE GnRH, so it recruits the body's own reproductive machinery rather than bypassing it.

KISS1R / GPR54 Signaling Cascade

- **Gαq/11 → PLCβ:** primary coupling generates IP3 + DAG and mobilizes intracellular Ca^{2+}
- **PKC → MAPK:** DAG-driven PKC phosphorylates ERK1/2 and p38 MAPK; the ERK1/2 cascade promotes GnRH gene expression and neuronal firing
- **Ca^{2+} / calmodulin:** the Ca^{2+} influx also engages calmodulin signaling, reinforcing GnRH gene expression
- **β-Arrestin (G-protein-independent):** β-arrestin-2 activates ERK while β-arrestin-1 inhibits it — a second signaling arm
- **NF-κB inhibition:** KP-10 blocks IKK phosphorylation and prevents p65 nuclear translocation — the basis of several non-reproductive (anti-metastatic) effects
- **Src dephosphorylation:** via Dusp18 recruitment to the GPR54 C-terminal PR motif — the basis of the bone-protective effect

HPG Axis: The Upstream Gatekeeper

KP-10 binds KISS1R on GnRH neurons in the arcuate nucleus and preoptic area, directly stimulating GnRH release into the portal circulation; GnRH then drives pituitary LH and FSH, which drive gonadal steroidogenesis. The proof that this is genuinely upstream: a GnRH antagonist blocks ALL kisspeptin effects. Because the signal enters at the top of the axis, downstream negative feedback remains intact — the response is physiological and self-limiting rather than an externally imposed hormone level.

The KNDy Neuron Model (pulse generation)

Kisspeptin works within a three-peptide system co-expressed in arcuate "KNDy" neurons: Kisspeptin, Neurokinin B (NKB, stimulatory), and Dynorphin (inhibitory). NKB starts the stimulatory phase and dynorphin terminates it; together they generate the pulsatile GnRH secretion the axis requires. Clinically, KP-10 can restore pulsatility in patients with NKB/NK3R loss-of-function — demonstrating it can drive the pulse generator directly.

Pleiotropic Effects Beyond Reproduction

Domain	Effect
Anti-metastatic	KISS1 is a metastasis-suppressor gene; KP-10 suppresses NF-κB → MMP-9, inhibits RhoA-driven migration, reverses EMT (↑E-cadherin, ↓Twist/N-cadherin)
Bone protection	GPR54 recruits Src + Dusp18; Dusp18 dephosphorylates Src(Y416), suppressing osteoclast formation (up to ~53% inhibition in vitro); a bone-targeted analog reduced OVX bone loss
Anti-angiogenic	Inhibits endothelial (HUVEC) migration and tube formation via Sp1/VEGF suppression
Metabolic	In HFD mice: normalized body weight, lowered glucose, ↑ GIP/GLP-1 cells, ↑ β-cell proliferation; ↓ lipogenesis / ↑ lipolysis in adipocytes (species/fragment-dependent; KP-13 may differ)
Neuroprotection	Preserves blood–brain barrier integrity post-stroke (Nrf2 / claudin-10 upregulation)

Mechanistic takeaway: KP-10's defining advantage is that it acts as the UPSTREAM switch of the reproductive axis — stimulating endogenous GnRH while preserving feedback — not as a replacement hormone. Its surprising breadth (anti-metastatic, bone, metabolic) traces to the same NF-κB / Src / Dusp18 signaling, but those effects remain preclinical.

3. Points of Clinical Relevance

1. Upstream action preserves feedback — the conceptual advantage over exogenous hormone

Because KP-10 stimulates the body's own GnRH neurons, the resulting LH/FSH/testosterone rise is physiological and self-limiting, and the HPG feedback loop stays intact. This is its central selling point versus exogenous testosterone or GnRH analogues, which override or suppress the native axis. It positions kisspeptin as a way to restore signaling rather than replace it.

2. Strong, reproducible effect in men — but the human data are IV

In healthy men, IV KP-10 reliably raises LH (peak ~12.4 IU/L at 1 μg/kg) and testosterone (~16.6 → 24.0 nmol/L) and increases LH pulse frequency, with pituitary reserve preserved. This is the best-validated kisspeptin effect — but it comes from IV bolus/infusion studies, not the SC route used in practice.

3. Marked sexual dimorphism — in women, menstrual phase determines the response

KP-10's effect in women is highly phase-dependent: robust in the preovulatory and luteal phases and in hypothalamic amenorrhea and post-menopause, but essentially absent in the follicular phase (KISS1R near-saturation) and suppressed in oral-contraceptive users. Any use in women must account for cycle phase; the same dose can do very different things at different times.

4. The blood-brain-barrier question is the central unknown for SC use

Dr. Seeds's key caveat: KP-54 crosses the blood–brain barrier but KP-10's penetration is limited, and there is no SC dataset confirming that the empirical 100–200 µg SC dose produces the LH changes seen with IV. Whether subcutaneous KP-10 reaches its hypothalamic target in a meaningful way is genuinely unresolved — a gap to disclose honestly to patients.

5. Very short half-life and tachyphylaxis dictate pulsatile, cycled dosing

With a ~4-minute half-life, KP-10 requires frequent/pulsatile dosing for sustained effect, and continuous or high-dose exposure causes tachyphylaxis (e.g. a paradoxical blunted response to a 3 µg/kg bolus; loss of response by day 14 of BID SC). Practically this drives multiple daily SC doses and 8–12 week cycles — mimicking the body's natural pulsatility rather than steady-state stimulation.

6. Pleiotropic promise is real but preclinical — and cardiovascular caution applies

The anti-metastatic, bone-protective, and metabolic effects are mechanistically compelling but remain in vitro/animal. Importantly, KP-10 is a vasoconstrictor at higher doses and may promote atherosclerotic plaque instability — so cardiovascular disease is a genuine caution, not a footnote. Do not extrapolate the pleiotropic benefits to clinical use yet.

4. General Dosing & Delivery Options

No FDA-approved dosing exists. The robust dose-response data are IV (clinical trials); SC dosing is extrapolated/empirical with no trials confirming it crosses the BBB or reproduces the IV LH response. For educational context only; WADA-prohibited in sport.

Men — IV Evidence vs SC Practice

Route / Protocol	Dose	Outcome
IV bolus	0.3 µg/kg	Significant LH rise within 30 min
IV bolus	1.0 µg/kg	Maximal LH (~12.4 IU/L)
IV bolus	3.0 µg/kg	Paradoxical BLUNTED response (desensitization threshold)
IV infusion	4.0 µg/kg/h × 22.5 h	LH 5.5 → 20.9 IU/L; no tachyphylaxis over 22.5 h
SC (empirical, off-label)	100–200 µg, 2–4×/day	Clinical-practice dosing; 8–12 week cycles; effect on LH not trial-confirmed

Women — Dose by Menstrual Phase

Phase / Population	Representative Dose	Response
Preovulatory	10 nmol/kg IV	Reliable LH/FSH elevation
Follicular	up to 10 nmol/kg IV	NO response (KISS1R near-saturation)

Phase / Population	Representative Dose	Response
Luteal	0.24 µg/kg IV	Immediate LH pulse
Post-menopausal	0.3 µg/kg IV	Enhanced sensitivity
Hypothalamic amenorrhea	6.4 µg/kg SC	Potent LH rise (up to ~24 IU/L)

Administration, Reconstitution & Cycling

- **Pulsatile dosing:** the ~4-min half-life means IV bolus gives rapid, brief onset; infusion sustains effect; SC absorbs more slowly — hence multiple daily SC doses in practice
- **Cycling:** 8–12 week cycles to mitigate tachyphylaxis; track LH over time and use pulsatile dosing if response wanes
- **Reconstitution (per slides):** 10 mg vial + 3.0 mL bacteriostatic water = 3.33 mg/mL; ~1 U on a U-100 syringe ≈ 33.3 µg
- **Storage:** lyophilized at −20°C; reconstituted at 2–8°C; avoid freeze–thaw cycles

5. Evidence Profile

Evidence tier distribution: unusually strong mechanistic and human PHYSIOLOGY data (multiple human IV trials in men and women, detailed receptor/structural biology) but NO efficacy RCTs for the empirical SC clinical use, no SC PK/BBB confirmation, and no human data for the pleiotropic (anti-cancer, bone, metabolic) effects. Reproductive-therapeutic outcome data are largely KP-54, not KP-10.

Human — Reproductive Endocrine (the strongest data)

- Men (George 2011): IV KP-10 raised LH (peak ~12.4 IU/L) and testosterone (16.6 → 24.0 nmol/L), increased LH pulse frequency; no tachyphylaxis over a 22.5 h infusion; 3 µg/kg bolus blunted (desensitization)
- Sexual dimorphism (Jayasena 2011; George 2012): robust in men; in women phase-dependent — preovulatory/luteal responsive, follicular not, post-menopausal enhanced
- Hypothalamic amenorrhea (Jayasena 2009): SC KP-10 stimulated gonadotropin secretion — a responsive clinical population
- NKB/NK3R loss-of-function (Young 2013): KP-10 restored pulsatile LH — proof it can drive the GnRH pulse generator

KP-10 vs KP-54 vs GnRH (head-to-head)

Parameter	KP-10	KP-54	GnRH
In vivo half-life	~4 min	~27.6 min	~4 min
BBB penetration	Limited	Yes	Yes
Relative potency (IV)	Reference	Higher LH AUC	~3× more potent than KP-10

Parameter	KP-10	KP-54	GnRH
Signature use	Pulsatile LH/FSH	IVF trigger	Standard axis stimulant

Preclinical — Pleiotropic (no human efficacy data)

- Anti-metastatic (in vitro/animal): NF-κB/MMP-9 suppression, RhoA inhibition, EMT reversal; KISS1 loss correlates with metastasis
- Bone (animal/in vitro): Src/Dusp18 osteoclast suppression; bone-targeted analog reduced OVX bone loss; acute osteocalcin rise in men
- Metabolic (animal): weight/glucose normalization and islet effects in HFD mice — no human metabolic RCTs

Safety (animal + human physiology)

- NOAEL ~1,000 µg/kg/day (14-day IV dog; >3,000× clinical dose); no organ/cardiac/hematologic toxicity; no ECG/BP/respiratory abnormalities
- Humans: no serious adverse events up to 3 µg/kg IV bolus; mild nausea, headache, flushing, injection-site reactions

Critical gaps: NO efficacy RCTs for the empirical SC protocol; no SC pharmacokinetics and no confirmation that SC KP-10 crosses the BBB or reproduces the IV LH response; no human data for anti-cancer, bone, or metabolic claims; reproductive-therapeutic outcomes (IVF) are KP-54, not KP-10; long-term safety unknown; and a real dose-dependent vasoconstriction / plaque-instability signal. WADA-prohibited; not FDA-approved.

6. Clinical Considerations

Contraindications

- **Hormone-sensitive cancers** (breast, prostate, endometrial with hormone dependence): avoid — LH/FSH/sex-steroid stimulation is undesirable
- **Cardiovascular disease / significant atherosclerosis:** vasoconstrictor effects and potential plaque instability — avoid or use extreme caution
- **Pregnancy:** kisspeptin is naturally elevated in pregnancy; exogenous use not studied — avoid
- **Competitive athletes:** WADA-prohibited (S2) since 2024

Cautions

- Women: response is menstrual-phase-dependent — dose and expectations must account for cycle phase / contraceptive use
- Tachyphylaxis with continuous or high-dose exposure — favor pulsatile, cycled dosing
- Source quality and the unconfirmed SC–BBB question argue for conservative, well-documented use

Drug Interactions

Formal interaction data are limited. GnRH antagonists abolish kisspeptin's effects (mechanistic). Coordinate cautiously with other agents acting on the HPG axis (exogenous testosterone, GnRH analogues, oral contraceptives — the last suppress the response). Document all concurrent hormonal therapy.

Monitoring Parameters

Parameter	Target / Note	Rationale
LH, FSH, testosterone, E2	Baseline + during treatment	Primary HPG-axis response
LH over time	Watch for declining response	Detect tachyphylaxis; guide pulsatile dosing
Bone markers	Osteocalcin, CTX, P1NP (if targeting bone)	Bone-effect monitoring
Cardiovascular status	BP, vascular risk review	Vasoconstriction / plaque-instability signal
Cancer screening	Age/risk-appropriate; before use	Hormone-sensitive malignancy risk

Cadence: baseline (HPG panel, cardiovascular and cancer-risk review, cycle phase in women), reassess hormone response and tolerability during each cycle while tracking LH for tachyphylaxis, and run 8–12 week cycles with breaks. Discontinue for any hormone-sensitive malignancy concern, cardiovascular deterioration, or confirmed pregnancy. Document route, dose, cycle, phase, and response.

Safety Profile

- Favorable in animal toxicology (NOAEL >1,000 µg/kg dog; no organ, cardiac, or hematologic toxicity) and in human IV studies (no SAEs; mild transient effects)
- Principal hazards: tachyphylaxis, dose-dependent vasoconstriction / plaque instability, and unknown long-term safety

Regulatory Status

Kisspeptin-10 is NOT FDA-approved (investigational only) and is on the WADA Prohibited List (S2: peptide hormones) as of 2024. Any human use is investigational/off-label and requires explicit, documented informed consent, including the unconfirmed SC–BBB question and the cardiovascular caution.

7. Final Note

As the first of three peptides in the Hormonal & Sexual Health group, Kisspeptin-10 is the right place to begin because it sits at the very top of the reproductive cascade. It is the upstream switch for GnRH: by stimulating the body's own GnRH neurons via KISS1R/GPR54, it raises LH, FSH, and downstream sex steroids while leaving the HPG feedback loop intact — a physiological, self-limiting mechanism that is conceptually distinct from, and in some ways preferable to, supplying exogenous testosterone or GnRH. Its human physiology is genuinely well characterized: a robust, reproducible LH/testosterone response in men, and a striking

sexual dimorphism in women in which menstrual phase determines whether the same dose does anything at all.

The honest framing is that the strongest evidence and the common real-world use do not yet line up. The compelling human data are intravenous; the empirical practice is 100–200 µg subcutaneously, several times daily, and there is no SC pharmacokinetic or efficacy dataset — and a real open question, emphasized by Dr. Seeds, about whether SC KP-10 crosses the blood–brain barrier to reach its target at all (KP-54 does; KP-10's penetration is limited). Add a ~4-minute half-life, predictable tachyphylaxis, a dose-dependent vasoconstriction/plaque signal, and WADA prohibition, and the practical picture is of a mechanistically elegant peptide whose clinical protocol remains unproven.

For the clinician, Kisspeptin-10 is best understood as a research-stage, upstream HPG modulator with excellent mechanistic and safety credentials but unsettled SC efficacy. Its pleiotropic anti-metastatic, bone, and metabolic effects are intriguing but entirely preclinical, and its reproductive-therapeutic track record (IVF) largely belongs to KP-54. Use — if at all — only investigationally, with attention to sex and menstrual phase, pulsatile cycled dosing, cardiovascular and cancer screening, and full informed consent.

Bottom line: The upstream gatekeeper of the reproductive axis and the first peptide in the Hormonal & Sexual Health group — a KISS1R/GPR54 agonist that stimulates endogenous GnRH and raises LH/FSH/testosterone while PRESERVING feedback. Strong human IV data in men; menstrual-phase-dependent in women; ~4-min half-life requiring pulsatile, cycled (8–12 wk) dosing. Major caveats: SC use (100–200 µg) is unproven and may not cross the BBB; tachyphylaxis and a vasoconstriction/plaque signal are real; pleiotropic and IVF data are preclinical or KP-54, respectively. NOT FDA-approved; WADA-prohibited. Research/investigational only.

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For educational and research purposes only. Not medical advice. Kisspeptin-10 is NOT FDA-approved (investigational only) and is on the WADA Prohibited List (S2) as of 2024. The strong human data are intravenous; the empirical subcutaneous protocol (100–200 µg) lacks pharmacokinetic/efficacy confirmation and may not cross the blood–brain barrier (unlike kisspeptin-54). It shows a dose-dependent vasoconstriction/plaque-instability signal, and its anti-cancer/bone/metabolic effects are preclinical. First of three peptides in the Hormonal & Sexual Health series. Based on lecture materials by William Seeds, MD — SSRP Institute | Cellular Medicine Education.