Kisspeptin-54

A Clinical Learning Guide for Medical Providers

Metastin • Full-Length Kisspeptin / KISS1R Agonist • Hormonal & Sexual Health (3 of 3)

Evidence base at a glance: The third and final peptide in the Hormonal & Sexual Health group — and the PARENT molecule of Kisspeptin-10 (guide 1). KP-54 is the full-length, major circulating kisspeptin and the master regulator of the reproductive axis. Three facts dominate: (1) it shares KP-10's upstream GnRH-stimulating mechanism but acts longer and crosses the blood–brain barrier (KP-10 does not) — a single SC dose sustains an LH surge for 12–14 HOURS vs minutes for KP-10; (2) that sustained-but-self-limiting surge makes it the standout clinical application of the whole group — an IVF oocyte-maturation trigger with near-ZERO ovarian hyperstimulation (OHSS), the strongest human data in this series (Phase 2, ~175 patients); and (3) it has a striking DUAL identity — the same molecule ("metastin") is a metastasis-suppressor across 15+ cancers. Its main limitation is tachyphylaxis with chronic dosing. NOT FDA-approved (investigational).

1. Peptide Profile

Name: Kisspeptin-54 (Metastin); the full-length active kisspeptin

Classification: KISS1R (GPR54) agonist; master regulator of the HPG axis. Dual identity — reproductive neuroendocrine peptide AND metastasis-suppressor gene product

Structure: 54-amino-acid peptide (~5.9 kDa) cleaved from a 145-aa precursor (KISS1 gene); the major circulating isoform. Shares the C-terminal RF-amide decapeptide required for KISS1R activation

Gene / Receptor: Gene KISS1; receptor KISS1R / GPR54, a Gαq/11-coupled GPCR (chr 19p13.3)

Half-life & duration: Plasma half-life ~27.6 min, BUT a single dose sustains LH release for 12–14 hours — vs ~4 min / 10–60 min for KP-10

BBB penetration: YES — KP-54 crosses the blood–brain barrier (KP-10 does not), enabling central + peripheral action

Routes: SC, IV (bolus/infusion), and intranasal (emerging); SC for the IVF-trigger application

Regulatory status: NOT FDA-approved — investigational only; FDA flags substantial safety risk for compounding

Completing the Hormonal & Sexual Health Group

This is the third and final peptide in the Hormonal & Sexual Health category, and it closes the loop opened by guide 1. Kisspeptin-10 (guide 1) is the minimal 10-amino-acid fragment of THIS molecule; PT-141 (guide 2) works on a completely different system (central melanocortin/dopamine "desire" circuitry). KP-54 is the full-length parent: same KISS1R/GnRH mechanism as KP-10 but longer-acting and brain-penetrant. Read together, KP-54 and KP-10 give a complete picture of upstream HPG-axis modulation — KP-54 for sustained, single-dose

surges (IVF triggering) and KP-10 for shorter pulsatile stimulation — while PT-141 addresses desire rather than the hormonal axis itself.

KP-54 vs KP-10: The Parent–Fragment Distinction

Both bind KISS1R and stimulate GnRH, but the differences are clinically decisive. KP-54 is longer (54 vs 10 aa), longer-acting (~28 vs ~4 min half-life; 12–14 h vs 10–60 min of LH release), reaches ~50× higher peak plasma levels at equimolar doses, and crosses the BBB. The practical division of labor: KP-54 is the form used as an IVF oocyte-maturation TRIGGER (one sustained surge), whereas KP-10 is used more for shorter pulsatile LH/FSH stimulation. Much of the strongest reproductive-therapeutic data in this whole series — IVF triggering especially — is KP-54 data and should not be assumed to transfer to KP-10.

2. Modes of Action & Mechanisms

KP-54 binds KISS1R (GPR54) on GnRH neurons and triggers the same Gq/11 cascade as KP-10, but its size, longer half-life, and BBB penetration give a more sustained, centrally-reinforced effect. The same KISS1/GPR54 signaling also underlies its separate identity as a metastasis suppressor.

KISS1R / GPR54 Signaling (shared with KP-10)

- **Gαq/11 → PLC → IP3 + DAG → Ca^{2+}:** mobilizes intracellular calcium, depolarizing GnRH neurons
- **PKC → MAPK; ERK1/2 and p38:** drives GnRH gene transcription and neuronal firing
- **β-arrestin-2 (G-protein-independent ERK):** a second signaling arm
- **NF-κB downregulation → MMP-9 suppression:** the link between signaling and the anti-metastatic identity

HPG Axis: Master Regulator (with central reinforcement)

KP-54 binds KISS1R on GnRH neurons in the arcuate nucleus and AVPV/preoptic area, causing persistent depolarization and GnRH release at the median eminence → pituitary LH/FSH → gonadal steroidogenesis, with feedback intact. Because KP-54 crosses the BBB, it can also engage GnRH neurons centrally (behind the barrier) — though Dr. Seeds notes the median eminence sits outside the BBB, so peripheral KP-54 may act there regardless. As with KP-10, a GnRH antagonist blocks all effects (confirming the upstream, GnRH-dependent mechanism), and GPR54-deficient humans/mice show hypogonadotropic hypogonadism and failed puberty — underscoring that this pathway is essential, not merely modulatory.

The Signature Feature: A Sustained but Self-Limiting LH Surge

The single most clinically important property is timing. A single KP-54 dose produces an LH surge lasting 12–14 hours — long enough to mature oocytes, but SELF-LIMITING, unlike hCG's ~7-day surge. This is precisely why KP-54 triggers egg maturation without the dangerous, prolonged ovarian stimulation that causes OHSS. The short half-life paired with a multi-hour functional surge is the mechanistic heart of its IVF advantage.

Dual Identity: Metastasis Suppression ("Metastin")

Anti-Metastatic Mechanism	Effect
Tumor dormancy	KISS1 was the first metastasis suppressor shown to induce dormancy at ectopic sites; inhibits autophagy in dormant cells
NF-κB / MMP-9	Suppresses MMP-9 via NF-κB inhibition (IκB stabilization) — reduces matrix degradation/invasion
PI3K-AKT-mTOR / VEGF	Inhibits the PI3K-AKT-mTOR axis and downregulates VEGF → suppresses angiogenesis
Metabolic (Warburg reversal)	Promotes OXPHOS over glycolysis; stabilizes PGC1α, inhibits hexokinase-II — a metabolic shift away from the tumor phenotype

KISS1 loss correlates with metastasis across 15+ cancers (melanoma, breast, pancreatic, ovarian, colorectal, and more). This is mechanistically compelling but entirely preclinical — no human cancer outcomes have been studied.

Mechanistic takeaway: KP-54 is the full-length kisspeptin — same upstream GnRH switch as KP-10, but longer-acting and brain-penetrant, producing a 12–14 h self-limiting LH surge that is the basis of its OHSS-free IVF triggering. Its second life as "metastin," a metastasis suppressor, is striking but remains preclinical.

3. Points of Clinical Relevance

1. The standout application is the OHSS-free IVF trigger — the strongest data in the series

KP-54's self-limiting 12–14 h LH surge matures oocytes while avoiding ovarian hyperstimulation syndrome — the dangerous complication of hCG triggering. Across Phase 2 trials (~175 patients), it produced high oocyte-maturation and live-birth rates with essentially ZERO moderate/severe OHSS. This is the most robust, clinically meaningful use of any peptide in this category.

2. It is the longer-acting, brain-penetrant counterpart to KP-10

Compared with KP-10 (guide 1), KP-54 lasts far longer (12–14 h vs 10–60 min of LH release) and crosses the blood–brain barrier. Practically, KP-54 suits single-dose sustained surges (triggering), while KP-10 suits shorter pulsatile stimulation. Dr. Seeds frames the two together as giving "incredible insight" into HPG-axis possibilities — they are complementary tools, not redundant.

3. Tachyphylaxis is the central limitation — and a useful guardrail

Chronic twice-daily dosing desensitizes the HPG axis within ~7–14 days (GPR54 downregulation, like GnRH-agonist desensitization), so single/acute and intermittent dosing (e.g. ~twice weekly) are favored, with pulsatile delivery under study. Dr. Seeds offers a practical tip: a rising heart rate can serve as a guardrail signaling desensitization — stop, and responsiveness returns over time, then resume.

4. Tachyphylaxis can be turned into therapy — the prostate-cancer angle

The same desensitization that limits chronic reproductive use can be exploited deliberately: continuous KP-54 can induce tachyphylaxis that suppresses LH and drops testosterone to castrate levels — a potential self-limiting alternative to GnRH agonists (e.g. leuprolide) for androgen deprivation in prostate cancer. This is a mechanistic rationale, not yet a proven therapy.

5. Psychosexual and diagnostic roles are emerging

Beyond reproduction, KP-54 modulates sexual and emotional brain processing on fMRI — enhancing limbic responses to sexual and bonding stimuli, deactivating self-monitoring regions, and attenuating negative mood (notably in those with lower baseline sexual quality of life), with greatest interest in HSDD. Diagnostically, a KP-54 test can distinguish constitutional delayed puberty from congenital hypogonadotropic hypogonadism (AUC 1.0), outperforming the GnRH test — a clean clinical use that doesn't depend on chronic dosing.

6. Favorable safety, but watch vasoconstriction and respect the evidence ceiling

Across 500+ subjects there were no serious adverse events and no significant BP/HR changes at gonadotropin-stimulating doses, with transient SC injection-site stinging in ~50%. However, kisspeptin is a documented vasoconstrictor at higher/continuous exposure (CVD caution), and the evidence ceiling is real: no Phase 3 trials, no multicenter replication, and no long-term (>8-week) safety data.

4. General Dosing & Delivery Options

No FDA-approved dosing exists; all protocols are from investigational trials (largely a single London group). The IVF-trigger dose has the best support; chronic dosing should be AVOIDED due to tachyphylaxis. For educational context only.

Dosing Protocols From Clinical Studies

Context	Route / Dose	Notes
IVF oocyte-maturation trigger	9.6 nmol/kg SC (single)	Optimal trigger dose; ~85% biochem / ~62% live-birth; near-zero OHSS
IVF — improved yield	9.6 nmol/kg SC + 9.6 at 10 h	Second dose at 10 h raised oocyte yield (71% vs 45%)
HPG stimulation (men)	0.3–1.0 nmol/kg IV bolus	Single dose; raises LH/FSH/testosterone
HA pulsatility restoration	0.01–1.0 nmol/kg/h IV × 8 h	Restores LH pulse frequency
HA acute stimulation	6.4 nmol/kg SC (single)	Robust LH (max ~24 IU/L)
Intranasal (emerging)	12.8 nmol/kg	Non-invasive; LH rise ~4.4 IU/L
Chronic twice-daily	6.4 nmol/kg BID	AVOID — tachyphylaxis by days 7–14

Tachyphylaxis & Administration Strategy

- **Single / acute dosing:** robust, predictable HPG response — the basis of triggering and diagnostics
- **Avoid chronic daily dosing:** progressive desensitization (GPR54 downregulation) by ~7–14 days
- **Intermittent (~twice weekly):** may partially preserve response; pulsatile (pump-style) delivery under investigation to mimic physiological KP-neuron firing
- **Guardrail:** a rising heart rate can signal desensitization — pause; responsiveness returns over time
- **Longer-acting analogs:** MVT-602 (synthetic KP agonist, t½ ~2 h; LH surge ~33 h at 3 mcg) is in development

5. Evidence Profile

Evidence tier distribution: the STRONGEST human evidence in the series — multiple Phase 2 IVF RCTs (~175 patients) plus human HPG-stimulation, fMRI psychosexual, and HA-pulsatility studies (N>500 total, no serious AEs) — but still NO Phase 3 trials, no multicenter replication, and the cancer/metabolic identities remain preclinical. Most reproductive trials come from a single London (Dhillo) group.

IVF Oocyte Maturation — Phase 2 (the strongest data)

Trial	N	Key Finding
Jayasena 2014 (JCI)	53	Single KP-54 triggers egg maturation; 23% clinical pregnancy
Abbara 2015 (JCEM)	60	95% oocyte maturation; live-birth rate 45%; ZERO OHSS
Abbara 2017 (Hum Reprod)	62	Second dose at 10 h: yield 71% vs 45%; zero OHSS

HPG Stimulation & Reproductive (moderate)

- Healthy men (Dhillo 2005): 90-min IV KP-54 raised LH (~10.8 vs ~4.2 U/L saline, p<0.001), with FSH/testosterone up; GH/prolactin/TSH unaffected; no BP/HR change
- Functional hypothalamic amenorrhea: acute SC raises LH/FSH; IV infusion restored LH pulsatility (~3× pulse frequency); chronic BID caused tachyphylaxis
- Healthy women: 1 week of twice-daily KP-54 did NOT abolish menstrual cyclicity

Psychosexual & Diagnostic (moderate)

- fMRI (Comninos 2017): enhanced limbic processing of sexual and bonding stimuli; attenuated negative mood
- HSDD (Mills 2023, men): deactivated self-monitoring regions while increasing arousal centers
- Delayed-puberty diagnosis (Phylactou 2025): KP-54 test distinguishes delayed puberty from CHH (AUC 1.0), outperforming the GnRH test

Metabolic & Oncologic (preclinical / early)

- Enhances glucose-stimulated insulin secretion in human islets (potential T2DM/hypogonadism link); no effect on appetite/food intake
- Metastasis suppression across 15+ cancers (KISS1 loss correlates with spread) — mechanistic/preclinical only, no human cancer outcomes

Critical gaps: NO Phase 3 trials and no multicenter replication — most reproductive data come from one London group; no long-term safety beyond ~8 weeks; the cancer-suppressor and metabolic identities are entirely preclinical (no human outcomes); tachyphylaxis limits chronic therapeutic use; and a documented vasoconstrictor effect warrants CVD caution. Not FDA-approved.

6. Clinical Considerations

Absolute Contraindications

- **Pregnancy:** avoid (kisspeptin is naturally elevated in pregnancy; exogenous use not studied)
- **Hormone-sensitive cancers:** avoid LH/FSH/sex-steroid stimulation
- **KISS1R (GPR54) mutations:** response depends on the mutation — may be absent or unpredictable

Relative Contraindications / Cautions

- Cardiovascular disease (vasoconstrictor effect at higher/continuous exposure); liver disease; pituitary tumors
- Chronic/continuous dosing — avoid due to tachyphylaxis (unless deliberate testosterone suppression is the goal, investigationally)

Drug Interactions

Formal interaction data are limited. GnRH antagonists abolish kisspeptin's effects (mechanistic). Coordinate carefully with other HPG-axis agents (GnRH analogues, exogenous sex steroids, hCG in the IVF setting). Document all concurrent hormonal therapy.

Monitoring Parameters

Setting	Monitoring	Purpose
Pre-treatment labs	LH, FSH, E2/testosterone, AMH, prolactin, TSH, CBC, BMP	Baseline axis + safety
Acute response	LH at 0, 30, 60, 120, 240 min; E2/testosterone at 4 h	Confirm HPG stimulation
IVF setting	Follicular ultrasound; OHSS screening at ET and ~day 11	Maturation + OHSS surveillance
Chronic / repeated	LH pulsatility; signs of tachyphylaxis by day 7–14 (incl. HR)	Detect desensitization

Cadence: baseline panel and cycle/CVD/cancer-risk review; acute LH/steroid timepoints to confirm response; in IVF, follicular ultrasound and OHSS screening; for any repeated dosing,

track LH pulsatility and tachyphylaxis (Dr. Seeds's heart-rate guardrail) through days 7–14. Avoid chronic daily use. Discontinue for any hormone-sensitive malignancy concern, cardiovascular deterioration, or confirmed pregnancy; document route, dose, and response.

Comparison: KP-54 vs KP-10 vs GnRH Agonist vs hCG

Feature	KP-54	KP-10	GnRH agonist	hCG
Half-life	~28 min	~4 min	Hours–days	~24–36 h
BBB penetration	Yes	No	Limited	No
LH surge duration	12–14 h	10–60 min	Variable	~7 days
OHSS risk (IVF)	Negligible	Unknown	Low	HIGH
FDA status	Investigational	Investigational	Approved	Approved

Safety Profile

- 500+ subjects, no serious adverse events; no significant BP/HR change; GH/prolactin/TSH unaffected at gonadotropin-stimulating doses
- Transient SC injection-site stinging (~50%); documented vasoconstrictor effect at higher/continuous exposure (CVD caution)
- Favorable short-term tolerability (rapid degradation + endogenous status); long-term safety beyond ~8 weeks unknown

Regulatory Status

Kisspeptin-54 is NOT FDA-approved (investigational only), and the FDA flags substantial safety risk for compounding. Any human use is investigational/off-label and requires explicit, documented informed consent — including the absence of Phase 3 data and the tachyphylaxis limitation. (As with other gonadotropin-active peptides, anti-doping rules may apply in sport — verify if relevant.)

7. Final Note

As the third and final peptide in the Hormonal & Sexual Health group, Kisspeptin-54 is a fitting capstone: it is the full-length parent of Kisspeptin-10 (guide 1) and the master regulator of the reproductive axis. It shares KP-10's upstream, feedback-preserving GnRH mechanism but acts longer and crosses the blood–brain barrier, producing a single-dose LH surge of 12–14 hours. That sustained-but-self-limiting surge is the key to its standout clinical role — an IVF oocyte-maturation trigger that matures eggs without the ovarian hyperstimulation that makes hCG dangerous — and it represents the strongest human evidence anywhere in this series. Its second identity as "metastin," a metastasis suppressor across many cancers, adds a genuinely intriguing but still preclinical dimension.

The honest framing is that breadth of mechanism outruns depth of proof. The IVF data are solid but Phase 2 and largely from a single London group, with no Phase 3 trials, no multicenter replication, and no long-term safety beyond about eight weeks. Tachyphylaxis with chronic dosing is the defining limitation — though, cleverly, it can be turned into a feature (deliberate

testosterone suppression as a self-limiting alternative to GnRH agonists in prostate cancer). The cancer and metabolic identities, however compelling mechanistically, have no human outcome data, and kisspeptin's vasoconstrictor effect warrants cardiovascular caution.

For the clinician, KP-54 is best understood as an investigational, upstream HPG modulator whose clearest value is acute and diagnostic — IVF triggering in OHSS-risk patients, single-dose HPG stimulation, and a clean diagnostic test for delayed puberty vs CHH — rather than chronic therapy. Taken together with KP-10 and PT-141, it completes a category that spans the full reproductive picture: the hormonal axis (KP-54 and KP-10) and the desire circuitry (PT-141). Use only investigationally, with appropriate screening, intermittent dosing, and full informed consent.

Bottom line: The full-length parent of KP-10 and the master HPG-axis regulator — longer-acting and brain-penetrant, with a 12–14 h self-limiting LH surge that makes it the standout OHSS-free IVF oocyte-maturation trigger (the strongest human data in the series, Phase 2, ~175 patients). Dual identity as metastasis suppressor ("metastin," preclinical). Main limit: tachyphylaxis with chronic dosing (avoid — or exploit it for testosterone suppression in prostate cancer). Favorable short-term safety; vasoconstrictor caution; no Phase 3, no long-term data. NOT FDA-approved. Third of three in the Hormonal & Sexual Health group — completing the picture alongside KP-10 (hormonal) and PT-141 (desire).

Selected References

1. Ohtaki T et al. Metastasis suppressor gene KiSS-1 encodes peptide ligand of a G-protein-coupled receptor. Nature. 2001;411(6837):613–617. [In Vitro]
2. Lee JH et al. KiSS-1, a novel human malignant melanoma metastasis-suppressor gene. J Natl Cancer Inst. 1996;88(23):1731–1737. [In Vitro]
3. Messager S et al. Kisspeptin directly stimulates GnRH release via GPR54. Proc Natl Acad Sci USA. 2005;102(5):1761–1766. [Animal / In Vitro]
4. Dhillo WS et al. Kisspeptin-54 stimulates the hypothalamic-pituitary-gonadal axis in human males. J Clin Endocrinol Metab. 2005;90(12):6609–6615. [Clinical Trial]
5. Jayasena CN et al. Kisspeptin-54 triggers egg maturation in women undergoing IVF. J Clin Invest. 2014;124(8):3667–3677. [Clinical Trial]
6. Abbara A et al. Efficacy of kisspeptin-54 to trigger oocyte maturation in women at high risk of OHSS during IVF. J Clin Endocrinol Metab. 2015;100(9):3322–3331. [Clinical Trial]
7. Abbara A et al. A second dose of kisspeptin-54 improves oocyte maturation in women at high risk of OHSS: a Phase 2 RCT. Hum Reprod. 2017;32(9):1915–1924. [Clinical Trial]
8. Comninos AN et al. Kisspeptin modulates sexual and emotional brain processing in humans. J Clin Invest. 2017;127(2):709–719. [Clinical Trial / fMRI]
9. Mills EG et al. Effects of kisspeptin on sexual brain processing and penile tumescence in men with HSDD: a randomized clinical trial. JAMA Netw Open. 2023;6(2):e2254313. [Clinical Trial]
10. d'Anglemont de Tassigny X et al. Mechanistic insights into the more potent effect of KP-54 vs KP-10 in vivo. PLoS One. 2017;12(5):e0176821. [Animal Study]
11. Jayasena CN et al. SC kisspeptin-54 acutely stimulates gonadotropin secretion in women with hypothalamic amenorrhea, but chronic administration causes tachyphylaxis. J Clin Endocrinol Metab. 2009;94(11):4315–4323. [Clinical Trial]
12. Jayasena CN et al. Increasing LH pulsatility in women with hypothalamic amenorrhoea using IV infusion of kisspeptin-54. J Clin Endocrinol Metab. 2014;99(6):E953–E961. [Clinical Trial]

13. Jayasena CN et al. Twice-daily SC kisspeptin-54 does not abolish menstrual cyclicity in healthy women. J Clin Endocrinol Metab. 2013;98(11):4464–4474. [Clinical Trial]
14. Izzi-Engbeaya C et al. The effects of kisspeptin on beta-cell function, serum metabolites and appetite in humans. Diabetes Obes Metab. 2018;20(12):2800–2810. [Clinical Trial]
15. Harihar S, Welch DR. KISS1 metastasis suppressor in tumor dormancy. Cancer Metastasis Rev. 2023;42(1):183–196. [Review]
16. Zhu N et al. The KiSS-1/GPR54 system: roles in physiological homeostasis and cancer biology. Genes Dis. 2022;9(1):28–40. [Review]

For educational and research purposes only. Not medical advice. Kisspeptin-54 is NOT FDA-approved (investigational only); the FDA flags substantial safety risk for compounding. Its strongest data are Phase 2 IVF-trigger trials from a single research group; there are no Phase 3 trials, no multicenter replication, and no long-term safety data, and its cancer/metabolic identities are preclinical. Chronic dosing causes tachyphylaxis. Third of three peptides in the Hormonal & Sexual Health series (parent molecule of Kisspeptin-10). Based on lecture materials by William Seeds, MD — SSRP Institute | Cellular Medicine Education.