

SORRELL MD

The 90-Day *Fertility* Protocol

Fertility is a vital sign. It reads out the health of two whole people — metabolic, hormonal, mitochondrial, inflammatory, and environmental — roughly 90 days after the fact. That lag is the problem and the opportunity. This is the full root-cause workup and correction plan for both partners, and what to do when optimization is not enough.

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CLINICAL REFERENCE — BOTH PARTNERS

62%

Decline in total sperm count among men worldwide, 1973–2018. The rate of decline has roughly doubled since 2000.

1 in 6

Adults who experience infertility in their lifetime, per the WHO's 2023 global estimate.

~50%

Of cases with a male factor contributing — yet the female partner still receives the overwhelming majority of the workup.

1.6

US total fertility rate, against a replacement rate of 2.1. A record low, and still falling.

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What is actually *happening*

Human reproductive capacity is deteriorating faster than any plausible genetic explanation allows. Whatever is driving it is **environmental, metabolic, and recent** — which is precisely why so much of it is modifiable.

The 2022 meta-regression by Levine and colleagues in *Human Reproduction Update* pooled 223 studies across 53 countries. Mean sperm concentration fell approximately 52% and total sperm count approximately 62% between 1973 and 2018, and the annual rate of decline more than doubled after the year 2000. The trend is not confined to Western populations, and it does not disappear when you adjust for abstinence time, collection method, or study quality.

Running alongside it: population-level testosterone declines independent of age and BMI, documented since Trivison's Massachusetts Male Aging Study analysis and reproduced in adolescents and young men. Rising maternal and paternal age. Obesity and insulin resistance in a majority of adults of reproductive age. And an exposure profile with no historical precedent — phthalate metabolites detectable in more than 95% of the US population on NHANES sampling, PFAS in roughly 97%, and microplastics now recovered from human testis, semen, placenta, and follicular fluid.

HOW TO READ THIS DOCUMENT

Nothing here claims that any single exposure caused any individual couple's infertility. The claim is narrower and more useful: a large fraction of what limits fertility today is *correctable physiology* — inflammation, oxidative stress, insulin resistance, hormonal signalling, micronutrient status, sleep, and toxic load — and almost none of it is measured before couples are routed into IVF.

That last point is the practical one. A standard fertility pathway measures ovarian reserve, checks the tubes, runs a basic semen analysis, and then escalates. It is superb at bypassing problems and largely uninterested in fixing them. Bypassing works — but it works considerably better on a couple whose biology has been repaired first, and for a meaningful number of couples it turns out not to be necessary at all.

The 90-day *window*

Both gametes take about three months to build. **Today's semen analysis reports on last winter.** The egg ovulating this month began its metabolically active maturation roughly 90 days ago. This is the single most important fact in the document, because it defines both the intervention window and the retest date.



Spermatogenesis runs 64–74 days, followed by 10–14 days of epididymal transit and maturation. Oocytes take longer overall — primordial follicles are recruited over months — but the gonadotropin-responsive, metabolically demanding phase from preantral follicle to ovulation is roughly 85–90 days. Interventions are therefore judged at 90 days, not at 3 weeks.

WHAT THIS CHANGES IN PRACTICE

Do not re-test at six weeks and conclude something failed. Do not start an IVF cycle three weeks after beginning correction and expect the substrate to have changed. And when a semen analysis comes back poor, always ask what happened *90 days ago* — a febrile illness, a course of steroids, a hot-tub habit, a training block, a bad stretch of sleep. A single bad sample is often a snapshot of a bad quarter, not a verdict.

Shared terrain: the *twelve levers*

Most of the workup is identical for both partners. Sperm and oocytes are both exquisitely sensitive to the same four insults — **oxidative stress, insulin resistance, inflammation, and impaired mitochondrial output** — because both are unusually energy-hungry cells with unusually exposed DNA. Run these twelve on both people, at the same time, on day one. Sex-specific divergences are called out inside each lever.

THE FRAMING ERROR TO AVOID

Male factor contributes in roughly half of cases, yet in most practices the woman is investigated first, investigated further, and treated regardless. Test both partners in parallel from the start. A normal female workup does not make the problem female, and a normal semen analysis by 2021 WHO criteria does not make the sperm good — see Part IV.

1. Inflammation, oxidative stress, and methylation

These three run together and are the mechanistic heart of the problem. Reactive oxygen species damage sperm membranes (which are loaded with polyunsaturated fatty acids and carry almost no cytoplasmic antioxidant defence) and fragment sperm DNA. In the oocyte, oxidative stress degrades spindle assembly and drives aneuploidy. Methylation status governs both DNA repair and the epigenetic imprinting laid down in the gamete — which is inherited.

MARKER	TARGET	WHAT IT TELLS YOU
hs-CRP	<1.0 mg/L	Systemic inflammatory tone. Repeat if >10 — that is acute illness, not baseline.
Homocysteine	<8 $\mu\text{mol/L}$	Methylation adequacy. Elevated levels track with sperm DNA fragmentation and recurrent loss.
F2-isoprostanes (8-iso-PGF ₂ α)	low–normal	Best-validated <i>in vivo</i> marker of lipid peroxidation. Urine, creatinine-normalized.
Urinary 8-OHdG	low–normal	Oxidative DNA damage. Correlates with sperm DFI.
Glutathione (RBC / whole blood)	upper half	Antioxidant reserve. Pair with the GSH:GSSG ratio if available.

MARKER	TARGET	WHAT IT TELLS YOU
GGT	<20 U/L	Cheap surrogate for oxidative and xenobiotic burden. Rises long before liver enzymes do.
Ferritin, fibrinogen, WBC differential	context	Ferritin doubles as an acute-phase reactant and an iron marker. Neutrophil:lymphocyte ratio <2.

All of these should be *normal*, not merely “not flagged.” Reference ranges describe a population that is increasingly unwell.

Correction. Find the source before reaching for antioxidants — visceral fat, glycemic load, dysbiosis, poor sleep, mold, alcohol, nicotine, overtraining, and untreated infection produce most of it. Then support: N-acetylcysteine 600–1200 mg, glycine, alpha-lipoic acid, sulforaphane (broccoli sprout extract, for NRF2 activation), and a genuinely high-polyphenol diet. For methylation: methylated or folinic folate, B12 to a serum level above 500 pg/mL with methylmalonic acid under 150 nmol/L, P5P, riboflavin (particularly with MTHFR C677T), betaine, and choline.

CAUTION

More antioxidant is not better. Sperm require a controlled amount of reactive oxygen species for capacitation and the acrosome reaction; over-suppression can worsen function. Dose to the marker, retest at 90 days, and stop chasing.

2. Insulin resistance

Hyperinsulinemia is the most consequential and most under-detected metabolic driver in both sexes. In women it raises ovarian theca-cell androgen production, suppresses SHBG (raising free androgen further), and disrupts ovulation — it is the engine of PCOS. In men it lowers total and free testosterone, raises aromatization to estradiol, and worsens motility and DNA fragmentation independent of BMI. A normal HbA1c does not exclude it.

TEST	TARGET	NOTES
Fasting insulin	<6 μ IU/mL	The single most useful number most panels omit.
HOMA-IR	<1.5	$(\text{fasting insulin} \times \text{fasting glucose}) \div 405$.
2-hour 75 g OGTT — glucose	<120 mg/dL	The definitive test. Draw insulin at 0/30/60/120 alongside.
1-hour OGTT glucose	<140 mg/dL	A 1-hour value >155 predicts future dysglycemia even with a normal 2-hour result.

TEST	TARGET	NOTES
Peak OGTT insulin	<40 μIU/mL	Reveals compensated resistance while glucose still looks perfect.
HbA1c	<5.4%	Insensitive on its own. Confounded by red-cell turnover and iron status.
Triglyceride : HDL ratio	<1.5	Free, on every lipid panel, and a decent proxy.

Correction. Protein-forward, low-glycemic-load eating; resistance training two to four times weekly plus post-meal walking; sleep repair; visceral fat reduction. Two weeks of continuous glucose monitoring is often more behaviourally persuasive than any lab result. Pharmacologic options where indicated: metformin, and myo-inositol with D-chiro-inositol in a 40:1 ratio (2 g / 50 mg twice daily), which restores ovulation in PCOS with comparable efficacy to metformin and better tolerability.

GLP-1 RECEPTOR AGONISTS AND CONCEPTION

These are excellent tools for the pre-conception phase and must be stopped before it ends. Manufacturer guidance for semaglutide is to discontinue at least **2 months before a planned pregnancy**; plan for a longer washout with extended-release agents. Separately, tirzepatide reduces oral contraceptive absorption, which matters for cycle timing. And rapid weight loss inside the 90-day window mobilizes lipophilic toxicants stored in adipose — time aggressive loss to *end* before the window begins, not to run through it.

3. Body composition and visceral fat

Adipose tissue is an endocrine organ. Visceral fat in particular is an aromatase factory that converts testosterone to estradiol, a source of inflammatory cytokines, and a reservoir for lipophilic endocrine disruptors. DEXA gives you the number that matters; BMI does not.

- **DEXA visceral adipose tissue <100 cm²** — the primary target for both partners.
- **Appendicular lean mass index** — men ≥7.5–8.0 kg/m², women ≥6.0–6.5 kg/m². Muscle is the glucose sink.
- **Body fat percentage** — roughly 12–20% in men, 21–28% in women.
- **5–10% weight loss** restores ovulation in a substantial fraction of women with PCOS and improves semen parameters in men with obesity.

COMMONLY MISSED — THE OTHER END OF THE CURVE

Too lean is a fertility problem, and in athletic women it is the one that gets celebrated instead of treated. Low energy availability — broadly under about 30 kcal/kg fat-free mass per day — suppresses GnRH pulsatility and produces functional hypothalamic amenorrhea, with low LH, low FSH, low estradiol, low T3, and often normal-looking routine labs. Screen for it whenever cycles are long, light, or absent in a lean, high-training-volume woman. The treatment is more food and less training, and it works.

4. Micronutrient status

Run a formal panel — NutrEval (Genova), SpectraCell, or the Quest micronutrient panel — rather than guessing from a multivitamin label. Intracellular and functional assays catch deficiencies that serum levels miss.

NUTRIENT	TARGET	WHY IT MATTERS HERE
Vitamin D, 25-OH	40–60 ng/mL	Receptors in testis, ovary, and endometrium. Deficiency tracks with lower IVF success.
Zinc (plasma or RBC)	90–120 µg/dL	Spermatogenesis, testosterone synthesis, oocyte meiotic competence.
Selenium	110–140 ng/mL	Glutathione peroxidase; sperm midpiece structure; thyroid conversion. Toxic above ~400.
Copper : zinc ratio	0.7–1.0	High copper with low zinc is a common and correctable oxidative pattern.
RBC magnesium	5.0–6.5 mg/dL	Serum magnesium is nearly useless. Involved in 300+ ATP-dependent reactions.
Ferritin	40–70 ng/mL (women)	Low iron stores are an established cause of ovulatory infertility. Avoid excess in men.
Omega-3 index	>8%	DHA is a structural requirement for sperm membrane fluidity and morphology.
RBC folate & B12	upper half	Methylation, DNA synthesis, imprinting.
Iodine (urinary)	100–200 µg/L	Thyroid substrate. Under-replaced in the US, over-replaced by enthusiasts.
Choline (intake)	550–930 mg/d	Under-dosed in almost every prenatal on the market. See Part VI.

5. Thyroid

Not on most fertility panels beyond a TSH, and it should be on every one. Subclinical hypothyroidism and thyroid autoimmunity both raise miscarriage risk, and thyroid dysfunction impairs spermatogenesis in men.

- **TSH <2.5 mIU/L** when actively trying to conceive.
 - **Free T4, free T3, reverse T3** — a normal TSH with poor peripheral conversion is common in the presence of inflammation, low selenium, low ferritin, or caloric restriction.
 - **TPO and thyroglobulin antibodies** — euthyroid women who are TPO-positive carry a higher miscarriage rate. Selenium 200 µg daily can reduce titers.
 - Treat subclinical hypothyroidism with levothyroxine if TSH is >2.5 with positive antibodies, or >4.0 regardless.
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6. Cortisol and stress physiology

A single morning cortisol tells you almost nothing. Use a **four-point diurnal curve** — waking, +30 minutes (the cortisol awakening response), afternoon, bedtime — by saliva, or a dried urine panel that also reports cortisone and downstream metabolites so you can distinguish low output from rapid clearance.

- **Healthy pattern:** a 50–100% rise 30 minutes after waking, a steady decline across the day, and a low bedtime value.
- **Problem patterns:** a flat curve (blunted CAR), an elevated evening value, or a high total with a normal shape.
- **Mechanism:** CRH and β-endorphin suppress GnRH pulsatility directly. Downstream you get lower LH amplitude, delayed or absent ovulation, luteal phase defects, elevated prolactin, and in men lower testosterone.

Correction. This is where most protocols get vague, so be concrete: fixed sleep and wake times, morning outdoor light, a defined training ceiling, HRV tracking to catch overreaching, and a structured practice — slow-paced breathing at around 5.5 breaths per minute, or a formal mind–body program. Domar’s trials of mind–body group programs in infertile women reported conception rates roughly double those of controls; this is one of the better-supported “soft” interventions in the field. Ashwagandha (KSM-66, 600 mg) has reasonable male RCT data for semen parameters and testosterone; use caution with thyroid autoimmunity and stop it once pregnant.

7. Sleep

Testosterone is largely produced during sleep, and LH pulsatility is sleep-entrained. Restricting healthy young men to five hours nightly for one week lowered daytime testosterone by 10–15% (Leproult and Van Cauter, *JAMA* 2011). Rotating shift work is associated with reduced fecundability in women and worse semen parameters in men.

- **7–9 hours, with a consistent schedule** — regularity matters roughly as much as duration.
- **Screen for obstructive sleep apnea** in both partners — STOP-BANG, then a home sleep test. Untreated OSA lowers testosterone, worsens insulin resistance, and raises oxidative stress. This is a frequent miss in men with unexplained low testosterone.
- **Melatonin** concentrates in follicular fluid and acts as a direct antioxidant in the oocyte; 3 mg nightly has supportive data for oocyte quality in IVF. Discuss timing and discontinue on conception unless specifically continued.

8. Mitochondrial function

The oocyte is the most mitochondria-dense cell in the body, carrying on the order of 100,000 mtDNA copies, and the meiotic spindle assembly that determines whether an embryo is euploid is ATP-dependent. Age-related decline in egg quality is, mechanistically, mitochondrial decline. In sperm, the midpiece mitochondria drive motility, and membrane potential tracks with both motility and DNA integrity.

- **Assessment:** Mitome or MitoSwab testing; organic acid testing (included in NutrEval) for citric acid cycle intermediates, fatty acid oxidation markers such as adipate and suberate, and hydroxymethylglutarate as a functional CoQ10 marker; lactate:pyruvate ratio.
- **VO₂max** is a practical whole-body proxy and a modifiable one.
- **Correction:** CoQ10 as ubiquinol 200–600 mg daily (600 mg is the dose used in the IVF oocyte-quality literature); zone 2 training plus a weekly VO₂max stimulus for mitochondrial biogenesis; sauna for heat-shock protein induction; alpha-lipoic acid; L-carnitine and acetyl-L-carnitine, particularly for sperm motility; creatine.

EVIDENCE NOTE — NAD⁺ PRECURSORS

Nicotinamide riboside and NMN restore oocyte quality impressively in aged mice. Human reproductive data do not yet exist. Worth discussing honestly as a plausible but unproven adjunct, not presenting as established.

9. The gut

A major and frequently unrecognized source of both inflammation and oxidative stress. Dysbiosis drives lipopolysaccharide translocation and systemic inflammatory tone; the estrobolome — the β -glucuronidase-producing fraction of the gut microbiome — modulates enterohepatic estrogen recirculation; and malabsorption quietly produces the zinc, B12, iron, and fat-soluble vitamin deficiencies described above.

- **Comprehensive stool analysis** — GI-MAP or GI Effects: calprotectin, secretory IgA, β -glucuronidase, pathogens, and commensal balance.
- **SIBO breath testing** where bloating, irregular stools, or unexplained nutrient deficiency are present.
- **Celiac serology** — **tTG-IgA with a total IgA** on both partners. Undiagnosed celiac disease is a genuine and correctable cause of unexplained infertility and recurrent loss, and it is missed constantly.
- **H. pylori** stool antigen where indicated — a common cause of iron and B12 depletion.

10. Toxic exposure

Take a written exposure inventory covering home, occupation, personal care, water, and diet. Then reduce the biggest sources rather than pursuing exhaustive testing.

EXPOSURE	WHERE IT COMES FROM	WHAT TO DO
Phthalates	Fragrance, PVC, flexible plastics, food packaging, personal care products	"Fragrance-free" across all personal care; glass and stainless for food; never microwave in plastic.
BPA / BPS	Can linings, thermal receipts, polycarbonate	Decline paper receipts; reduce canned foods; replace plastic food storage.
PFAS	Non-stick cookware, stain and water repellents, fast-food packaging, drinking water	Check the local water report; install reverse osmosis or certified filtration; replace non-stick with stainless or cast iron. Serum PFAS panels are available.
Pesticide residue	Conventional produce, especially the high-residue group	The EARTH cohort linked high-pesticide-residue produce intake to lower total sperm count and lower live birth in ART. Buy organic for the highest-residue items.
Heavy metals	Cadmium (tobacco), lead (older housing, water), mercury (large fish), arsenic (rice)	Red-cell metals and unprovoked urine. Do not use provoked chelation challenge testing.

EXPOSURE	WHERE IT COMES FROM	WHAT TO DO
Nicotine & cannabis	All forms, including vaping and pouches	Stop. Nicotine is a cadmium vector and directly impairs both gametes; THC lowers sperm counts and disrupts endocannabinoid signalling at implantation.
Alcohol	—	Men: semen quality declines above roughly 5 drinks weekly. Women: no defensible amount inside the conception window.
Air quality	PM2.5, traffic, wildfire smoke, gas stoves	PM2.5 exposure tracks with lower sperm quality and lower IVF success. HEPA filtration in the bedroom; range hood vented outside.
Mold & mycotoxins	Water-damaged buildings	Assess the building first (ERMI / HERTSMI-2). Urinary mycotoxin testing is poorly standardized — remediate the environment rather than chasing the assay.

11. Exercise, sauna, and heat

Exercise has a clear dose–response optimum in fertility, and both tails are real.

THE PRESCRIPTION

- Resistance training 2–4× weekly — the strongest lever on insulin sensitivity and lean mass.
- Zone 2 aerobic work, 150–180 min weekly, for mitochondrial density.
- One weekly VO₂max session.
- Daily movement and post-meal walks.

THE CEILINGS

- **Men:** very high-volume endurance training, and cycling in particular, is associated with lower sperm concentration — saddle pressure plus scrotal heat.
- **Women:** in lean women with a normal BMI, more than about 5 hours weekly of vigorous exercise has been associated with *reduced* fecundability. In women with overweight or PCOS the same volume helps.

SAUNA — AND THE ONE NON-NEGOTIABLE FOR MEN

Sauna is genuinely valuable: cardiovascular benefit, heat-shock protein induction, mitochondrial biogenesis, HRV and stress recovery. Four to seven sessions weekly, 15–20 minutes at 175–195°F.

Men must cool the testes. Scrotal temperature has to sit 2–4°C below core, and heat exposure suppresses spermatogenesis: Garolla's 2013 study found that two 15-minute sauna sessions weekly for three months significantly reduced sperm count and motility, reversing over about six months. Ice or a cold plunge on the scrotum immediately afterward, and if parameters are borderline, drop *all* heat — sauna, hot tubs, seat heaters, laptops on the lap, tight underwear — for one full 90-day cycle and retest before concluding anything.

Women can use sauna freely pre-conception, but should avoid hyperthermia once conception is possible — core temperature above 102°F in the first trimester raises neural tube defect risk. Practically: stop sauna, hot tubs, and hot yoga at ovulation in any cycle you are trying.

12. Genetics — two different questions

Keep these separate, because they answer different things and one of them is guideline-mandated.

PATHWAY / FUNCTIONAL PANELS

3X4 Genetics or IntellxxDNA. These inform *how* you personalize: methylation (MTHFR, MTRR, COMT), detoxification capacity (GST M1/T1, NQO1, CYP1B1), inflammatory tendency, lipid handling, and vitamin D receptor variants. Useful for tailoring nutrients and exposure priorities. Not diagnostic.

CLINICAL GENETIC TESTING

- **Expanded carrier screening** — both partners.
- **Karyotype** — both partners with recurrent pregnancy loss or severe male factor.
- **Y-chromosome microdeletion and CFTR** — severe oligospermia or azoospermia.
- **FMR1 premutation (fragile X)** — any woman with diminished ovarian reserve or primary ovarian insufficiency. Routinely omitted.
- **Antiphospholipid and thrombophilia panel** — recurrent loss. Treatable, and missed constantly.

The *male* track

MEN Everything in Part III applies. What follows is additional.

Semen analysis — and why “normal” is misleading

Two samples, collected 2–4 weeks apart, after 2–5 days of abstinence, with consistent collection method. One sample is not a data point; intra-individual variability is enormous.

PARAMETER	WHO 2021 FLOOR	OPTIMAL TARGET
Volume	1.4 mL	>2.0 mL
Concentration	16 M/mL	>50 M/mL
Total sperm count	39 M	>100 M
Total motility	42%	>60%
Progressive motility	30%	>50%
Total motile count	—	>40–50 M
Normal morphology (Kruger)	4%	>6–8%
Vitality	54%	>70%
Peroxidase-positive leukocytes	<1 M/mL	absent

The WHO 6th edition values are the 5th percentile of men who conceived within twelve months. They are a floor below which fertility is clearly impaired — not a target, and not evidence that sperm are healthy. A man at the 6th percentile is “normal” and has a problem.

DNA fragmentation — the test standard workups skip

Sperm can look entirely normal on a conventional analysis and carry badly fragmented DNA. Fragmentation is the most direct readout of the oxidative stress described in Part III, and it predicts what the count does not: time to natural conception, miscarriage risk, and ICSI outcome.

- **DFI <15%** — excellent. **15–25%** — moderate, worth correcting. **>25%** — associated with reduced natural conception, higher miscarriage rates, and poorer ART outcomes.
- **Legacy** is a reasonable first-line route — at-home collection, semen analysis with DNA fragmentation, and integrated cryopreservation, which removes the main barrier to men actually getting tested.
- Confirm any abnormal at-home morphology result at a CAP-accredited andrology lab before acting on it; morphology in particular is method- and reader-sensitive.
- Consider **MiOXSYS** seminal oxidation-reduction potential (abnormal above roughly 1.34 mV per 10⁶ sperm/mL) to measure the oxidative stress directly rather than inferring it.
- **Shorten abstinence.** Two to three days is usually optimal; abstinence beyond five days raises DFI as sperm sit in the epididymis accumulating oxidative damage. This alone moves the number for some men.

Hormones

Draw between 7 and 10 a.m., fasted, and confirm an abnormal total testosterone on a second morning before acting. Use LC-MS/MS for testosterone and a sensitive assay for estradiol; immunoassay estradiol is unreliable in men.

MARKER	OPTIMAL	INTERPRETATION
Total testosterone	600–900 ng/dL	Serum T is a poor proxy for intratesticular T, which must run 50–100× higher for spermatogenesis.
Free testosterone	15–25 ng/dL	Equilibrium dialysis, not a calculated index.
SHBG	20–50 nmol/L	Low SHBG points to insulin resistance; high SHBG to thyroid excess or liver issues.
LH / FSH	3–8 / 2–8 IU/L	Low with low T = secondary (correctable). High FSH with low T = primary testicular failure.
Estradiol (sensitive)	20–35 pg/mL	Required for spermatogenesis and bone. Excess suppresses the axis and impairs sperm.
T : E2 ratio	>10 : 1	ng/dL to pg/mL. A low ratio is the signature of excess aromatase activity from visceral fat.
Prolactin	<15 ng/mL	Review medications above 25. Above 50–100, image the pituitary.

MARKER	OPTIMAL	INTERPRETATION
DHEA-S	upper-mid for age	Adrenal reserve; falls with chronic HPA load.
DHT	30–85 ng/dL	Suppressed on finasteride or dutasteride — see below.
Inhibin B	context	Sertoli-cell marker; useful with FSH in azoospermia.

TESTOSTERONE REPLACEMENT IS CONTRAINDICATED WHILE TRYING TO CONCEIVE

Exogenous testosterone suppresses LH, which collapses intratesticular testosterone, which stops spermatogenesis. It renders the majority of men azoospermic within four to six months — it has literally been studied as a male contraceptive. Recovery after stopping takes 3 to 12 months and is not always complete. This includes prescribed TRT, pellets, and anything obtained privately.

What to use instead. Restore the signal rather than replace the hormone:

- **Enclomiphene 12.5–25 mg daily, or clomiphene citrate 25 mg every other day up to 25–50 mg daily** — selective estrogen receptor modulation at the hypothalamus raises endogenous LH and FSH, and therefore intratesticular testosterone. Enclomiphene is the isolated trans-isomer and avoids zuclophene's long half-life and estrogenic side effects; note it is not FDA-approved and is compounded. Clomiphene is FDA-approved for women and used off-label in men.
- **hCG 1500 IU subcutaneously 2–3× weekly** where an LH-analogue effect is needed directly.
- **FSH / hMG** where spermatogenesis remains impaired with low-normal FSH.
- **Anastrozole 0.5–1 mg one to three times weekly** — only for genuinely elevated estradiol with a low T:E2 ratio, usually in obesity. Do not crush estradiol; it is required for spermatogenesis, libido, and bone.
- **Cabergoline** for confirmed hyperprolactinemia.
- Monitor testosterone, estradiol, LH/FSH, hematocrit, and a repeat semen analysis at 90 days.

The physical examination — and varicocele

COMMONLY MISSED — AND IT IS THE BIGGEST ONE

Varicocele is the most common correctable cause of male infertility and it is absent from most optimization protocols entirely. It is present in roughly 15% of all men, about 40% of men with primary infertility, and up to 80% of men with secondary infertility. The mechanism is exactly the one this document is built around: venous stasis raises scrotal temperature and generates oxidative stress, which fragments sperm DNA. Repair improves semen parameters and DNA fragmentation in appropriately selected men.

Do this: a proper scrotal exam standing, with Valsalva, plus scrotal ultrasound with Doppler. Also record testicular volume — below 15 mL by orchidometer suggests impaired spermatogenesis — and screen for masses, since testicular cancer is over-represented in infertile men.

Infection, obstruction, and mechanics

- **Leukocytospermia** (>1 million peroxidase-positive white cells/mL) — investigate and treat; it is a potent local oxidative stressor.
- **Semen culture and STI screen** — chlamydia, gonorrhea, and where relevant *Mycoplasma genitalium* and *Ureaplasma*.
- **Post-ejaculatory urinalysis** if volume is low — retrograde ejaculation is easy to find and treatable.
- **Anti-sperm antibodies** after vasectomy reversal, testicular trauma, or infection.
- **Erectile and ejaculatory function, and actual timing** — ask directly. Intercourse every 1–2 days across the fertile window; a surprising number of “infertility” workups resolve here.
- **Lubricant** — most commercial lubricants are spermatotoxic. Use a fertility-formulated product (Pre-Seed, Conceive Plus) or mineral or canola oil.

Medication and history review

- **Finasteride / dutasteride** — reduce semen volume, count, and motility; stop and allow a full 90-day cycle.
- **SSRIs** — raise prolactin, cause ejaculatory dysfunction, and are associated with increased DNA fragmentation.
- **Prior or current anabolic steroid use** — ask specifically and without judgement; it is common and it is the answer more often than expected.

- Opioids, gabapentinoids, sulfasalazine, colchicine, cimetidine, ketoconazole, chemotherapy history.
- **Any febrile illness in the last 90 days** — a single fever can wreck a semen analysis. Retest rather than react.

Targeted supplementation

CORE STACK

- **Needed Sperm Support+** — a well-formulated base covering the male-specific antioxidant and micronutrient set.
- **Comprehensive multivitamin**
- **CoQ10 (ubiquinol) 200–400 mg**, up to 600 mg where mitochondrial markers are poor
- **Omega-3, 2 g EPA + DHA** — DHA specifically improves morphology and membrane fluidity

ADD BY INDICATION

- L-carnitine 2 g + acetyl-L-carnitine 1 g — motility
- Zinc 25–30 mg; selenium 100–200 µg
- Vitamin C 500–1000 mg; vitamin E 200–400 IU
- NAC 600–1200 mg — elevated DFI or oxidative markers
- Lycopene 6–20 mg — morphology
- Vitamin D3 to a level of 40–60 ng/mL
- Ashwagandha KSM-66 600 mg — stress, testosterone, semen parameters

EVIDENCE NOTE — KEEP SUPPLEMENTS IN PROPORTION

The MOXI randomized trial (2020) found that an antioxidant formulation did not improve semen parameters or DNA fragmentation versus placebo in men with male-factor infertility, and the FAZST trial found folic acid plus zinc did not improve semen quality or live birth. This is not an argument against correcting a measured deficiency — it is an argument against supplements as the plan. Heat, varicocele, visceral fat, sleep, nicotine, alcohol, and medication review move the numbers. Supplements are the last ten percent.

Cryopreservation as insurance

If counts are low, declining, or about to be exposed to any intervention with reproductive risk, bank sperm first. It is inexpensive relative to everything downstream, and it converts a possible catastrophe into a manageable one. Legacy and standard andrology labs both do this.

The *female* track

WOMEN

Everything in Part III applies. What follows is additional.

Ovarian reserve

- **AMH** — drawn any cycle day. Roughly 1.0–4.0 ng/mL in the normal reproductive range; below 1.0 suggests diminished reserve; above 4–5 raises the question of PCOS.
- **Antral follicle count** by transvaginal ultrasound on cycle day 2–5. Ten to twenty total follicles is a typical normal range and it correlates with AMH.
- **FSH and estradiol on cycle day 2–3** — FSH under 10 mIU/L, and interpret it only alongside estradiol, because an early rise in estradiol suppresses FSH and hides diminished reserve.

HOW TO INTERPRET AMH WITHOUT CAUSING UNNECESSARY PANIC

AMH predicts *response to ovarian stimulation*. It is a much weaker predictor of natural conception. In the study by Steiner and colleagues (*JAMA*, 2017), women aged 30–44 with low AMH did not have meaningfully lower natural fecundability than women with normal AMH. A low AMH means fewer eggs are available to recruit in a cycle, not that the remaining ones are bad, and it should inform urgency and ART planning — not despair.

Tubes, cavity, and endometrium

- **Transvaginal ultrasound** — uterine anatomy, fibroids, polyps, ovarian cysts, endometriomas, and features of adenomyosis.
- **Tubal patency** — hysterosalpingography, or HyFoSy (hysterosalpingo-foam sonography), which avoids radiation. Note that tubal flushing itself appears therapeutic: oil-based contrast HSG increased ongoing pregnancy rates in the H2Oil trial.
- **Saline infusion sonohysterogram** for the cavity, with hysteroscopy as the definitive assessment where suspicion is high.
- **Endometrium** — a trilaminar pattern with a mid-cycle thickness of at least 7–8 mm. A persistently thin lining warrants investigation of prior instrumentation, chronic infection, and blood flow.

- **Chlamydia antibody titer** as a low-cost screen for prior tubal damage.

COMMONLY MISSED — CHRONIC ENDOMETRITIS

A low-grade, usually asymptomatic endometrial infection identified by CD138 immunohistochemistry on endometrial biopsy. It is found in a substantial proportion of women with recurrent implantation failure or recurrent loss, it is diagnosable in one biopsy, and it is treated with a course of antibiotics. It is almost never looked for.

THE LARGEST OMISSION IN MOST FERTILITY WORKUPS — ENDOMETRIOSIS

Endometriosis affects roughly 10% of reproductive-age women and 25–50% of women with infertility, and the average delay from first symptom to diagnosis is still seven to ten years. Ask directly about dysmenorrhea that stops normal activity, deep dyspareunia, cyclical bowel or bladder pain, heavy bleeding, and cyclical fatigue — a normal pelvic ultrasound does not exclude it. Escalate to expert transvaginal ultrasound using a deep-endometriosis protocol, or pelvic MRI, with laparoscopy as the definitive answer. **Adenomyosis** belongs in the same conversation: increasingly recognized, associated with implantation failure and loss, and visible to a sonographer who is looking for it.

PCOS evaluation

Rotterdam criteria — two of three: oligo- or anovulation; clinical or biochemical hyperandrogenism; polycystic ovarian morphology (antral follicle count ≥ 20 per ovary or ovarian volume ≥ 10 mL). The 2023 international guideline permits AMH to substitute for ultrasound in adults.

- **Exclude the mimics before labelling it PCOS:** thyroid disease; hyperprolactinemia; non-classic congenital adrenal hyperplasia (follicular-phase 17-hydroxyprogesterone under 200 ng/dL, with ACTH stimulation testing between 200 and 400); Cushing's syndrome if features are present; and an androgen-secreting tumor if total testosterone exceeds roughly 150–200 ng/dL or DHEA-S exceeds 700 $\mu\text{g/dL}$.
- **Lean PCOS is still metabolic** — a majority of these women are insulin resistant despite a normal BMI. Run the OGTT with insulins regardless of body habitus.
- **Treatment:** myo-inositol 2 g with D-chiro-inositol 50 mg twice daily; metformin; 5–10% weight loss where relevant; resistance training; vitamin D repletion; NAC; berberine. **Letrozole is first-line for ovulation induction** and produced higher live birth rates than clomiphene in PCOS (Legro, *NEJM* 2014). Spironolactone is effective for androgenic symptoms but is teratogenic — not while trying.

Hormones — and the timing that makes them mean anything

Female hormone results are close to uninterpretable without a cycle day attached.

Anchor the luteal draw to a *confirmed* ovulation, not to "day 21," which is only correct in a textbook 28-day cycle.

WHEN	WHAT TO DRAW	TARGETS AND NOTES
Cycle day 2–5 (early follicular)	FSH, LH, estradiol, total & free testosterone, DHEA-S, SHBG, prolactin, 17-OHP	FSH <10 with E2 <50 pg/mL. An LH:FSH ratio above 2 supports PCOS. Prolactin <20 ng/mL — draw it fasting, mid-morning, without prior exercise or breast stimulation, and repeat before acting on it.
Any day	AMH, TSH, free T4, free T3, TPO & Tg antibodies, hs-CRP, homocysteine, insulin, ferritin, vitamin D	TSH <2.5 mIU/L when trying. See Parts III.5 and III.4.
7 days after confirmed ovulation	Progesterone, estradiol	Progesterone >10 ng/mL confirms ovulation occurred; >15–20 is more reassuring for luteal adequacy. Progesterone is pulsatile, so a single low value is weak evidence.
Across the luteal phase	Urinary PdG (e.g. Proov), BBT, LH strips, cervical mucus	Serial PdG across days 7–10 post-ovulation assesses the whole implantation window rather than one pulse. A luteal phase shorter than 10 days is a signal in itself.

Progesterone support — and what it can and cannot fix

- **Micronized progesterone** 100–200 mg vaginally, or 200 mg orally at bedtime, started 2–3 days after *confirmed* ovulation and continued to menses — or through weeks 10–12 if pregnancy occurs.
- **Never start it before ovulation is confirmed.** Progesterone given in the follicular phase can suppress the LH surge and prevent the ovulation you are trying to support.
- **Treat the cause, not only the number.** A luteal phase defect is usually downstream of a poor follicular phase — hypothyroidism, hyperprolactinemia, insulin resistance, HPA-axis load, or low energy availability. The corpus luteum is built from the follicle that ovulated; fix the follicle.

EVIDENCE NOTE

The PROMISE and PRISM trials found that progesterone did not improve live birth in unselected women with recurrent miscarriage, but did improve live birth in the subgroup with three or more prior losses *and* early pregnancy bleeding. Use it deliberately in the right patient rather than reflexively in everyone.

Recurrent loss and implantation failure

Two or more losses changes the workup. Add, in parallel with everything above:

- **Antiphospholipid antibodies** — lupus anticoagulant, anticardiolipin, and anti- β 2-glycoprotein I, repeated at 12 weeks. Treatable, and one of the highest-yield tests in the workup.
- **Karyotype** on both partners; consider products of conception testing.
- **Uterine cavity assessment** — septum, submucosal fibroid, adhesions, polyp.
- **Thyroid antibodies and TSH; HbA1c; celiac serology; prolactin.**
- **Chronic endometritis** (CD138) and reproductive tract microbiome assessment — endometrial and vaginal *Lactobacillus* dominance is associated with better implantation.
- **Sperm DNA fragmentation on the male partner.** Miscarriage is not a female-only investigation, and DFI is one of the few paternal factors with a clear association.

Targeted supplementation

CORE STACK

- **Needed Prenatal Multi** — started at least 3 months before conception
- **Needed Egg Quality Support**
- **CoQ10 (ubiquinol) 200–600 mg** — 600 mg is the oocyte-quality dose
- **Omega-3** with at least 500–1000 mg DHA
- **Folate 800 μ g–1 mg** as methylfolate or folic acid — in place before neural tube closure at day 28, which is before most women know they are pregnant

ADD BY INDICATION

- Choline 550 mg — see Part VI; most prenats badly under-dose it
- Vitamin D3 to 40–60 ng/mL; iodine 150 μ g
- Iron to a ferritin of 40–70 ng/mL
- Magnesium glycinate 200–400 mg
- Myo-inositol / D-chiro-inositol — PCOS
- NAC — PCOS, endometriosis, elevated oxidative markers
- Melatonin 3 mg — oocyte quality, particularly around IVF
- DHEA 25 mg three times daily — diminished ovarian reserve; evidence is mixed, monitor androgens

STOP OR AVOID

Retinol above 10,000 IU daily (teratogenic); isotretinoin; statins; methotrexate; valproate; spironolactone; GLP-1 receptor agonists per the washout above; unregulated “fertility” herbal blends. Vitex may help luteal phase and mild hyperprolactinemia but interacts with fertility medications — do not combine without supervision. Chronic NSAID use around ovulation can inhibit follicle rupture.

Commonly *missed*

Everything in this part is either cheap, high-yield, or both — and routinely left out of otherwise thorough workups. Each is expanded in the relevant section above.

BOTH PARTNERS

- **Full thyroid panel with antibodies**, not a lone TSH — and a TTC target of TSH <2.5.
- **Celiac serology** (tTG-IgA with total IgA) — a real, correctable cause of unexplained infertility and recurrent loss.
- **Obstructive sleep apnea screening** — a frequent hidden driver of low testosterone, insulin resistance, and oxidative stress.
- **Periodontal disease.** Periodontitis is associated with longer time to conception and with adverse pregnancy outcomes. A dental cleaning and treatment of active disease belongs in the pre-conception plan. Almost nobody asks.
- **A full medication and supplement audit** — including a GLP-1 washout of at least two months, stopping statins and isotretinoin, and reviewing finasteride, SSRIs, NSAIDs, and immunosuppressants.
- **STI screening** on both partners.
- **Expanded carrier screening** on both partners.
- **Intercourse timing and frequency**, the fertile window, and lubricant choice — the most basic variable and one that is regularly skipped out of awkwardness.
- **Energy availability** — under-eating and over-training suppress the reproductive axis in both sexes and are easy to mistake for discipline.
- **Blood pressure, lipids, and a general pre-pregnancy safety baseline.** The goal is not conception; it is a healthy pregnancy and a healthy child.
- **Fertility preservation as insurance** — sperm banking, or egg or embryo freezing — considered early rather than after a year of trying.
- **Test both partners simultaneously.** The most common structural error in the whole field.

MEN — ADDITIONS TO YOUR LIST

- **Varicocele.** Scrotal exam standing with Valsalva, plus Doppler ultrasound. The single highest-yield omission.

- **Testicular volume and a mass exam** — infertile men carry elevated testicular cancer risk.
- **Abstinence interval of 2–3 days** before collection; longer intervals raise DNA fragmentation.
- **Leukocytospermia, semen culture, and post-ejaculatory urinalysis** for low volume.
- **Anti-sperm antibodies** after reversal, trauma, or infection.
- **Karyotype, Y-chromosome microdeletion, and CFTR** for severe oligospermia or azoospermia.
- **Any febrile illness in the previous 90 days** — retest rather than react.
- **Prior anabolic steroid use** — ask explicitly.
- **Seminal oxidation-reduction potential (MiOXSYS)** to measure oxidative stress in semen directly.

WOMEN — ADDITIONS TO YOUR LIST

- **Endometriosis and adenomyosis.** The largest omission on the female side. A normal routine ultrasound does not exclude either.
- **Chronic endometritis** — CD138 immunohistochemistry on endometrial biopsy; antibiotic-treatable.
- **Reproductive tract microbiome** — endometrial and vaginal *Lactobacillus* dominance.
- **Non-classic congenital adrenal hyperplasia** — follicular-phase 17-OHP, before settling on a PCOS label.
- **FMR1 (fragile X) premutation** in diminished ovarian reserve or primary ovarian insufficiency.
- **Antiphospholipid and thrombophilia testing** with recurrent loss.
- **Structural review** — submucosal fibroids, uterine septum, intrauterine adhesions, endometrial polyps.
- **Confirmed ovulation**, not assumed ovulation — and luteal draws anchored to it.
- **Immunity status** — rubella and varicella titers, hepatitis B, Tdap, before conception rather than during.
- **Choline 550 mg daily.** Critical for fetal neurodevelopment and placental function, and dramatically under-dosed in most prenatal formulations — check the actual label, not the marketing.

The 90-day *sequence*

Both partners run this together, starting the same week.

- 1 **Weeks 0–2 — Measure everything at once.** Full lab panel on both partners (Appendix). Two semen analyses with DNA fragmentation. Female imaging and cycle-timed draws scheduled to the actual cycle. Four-point cortisol. Body composition by DEXA. Written exposure inventory and full medication audit. Scrotal exam and ultrasound.
- 2 **Weeks 2–4 — Remove the big drivers before adding anything.** Stop nicotine, cannabis, and alcohol. Stop testosterone, finasteride, statins, and anything on the avoid list; begin the GLP-1 washout. Eliminate scrotal heat entirely for men. Fix the sleep schedule and treat sleep apnea. Set the training ceiling. Start the core supplement stack and correct the obvious deficiencies.
- 3 **Weeks 4–12 — Correct what the labs showed.** Insulin resistance, thyroid, hormonal signalling (enclomiphene or hCG in men; ovulation support or progesterone in women), gut treatment, micronutrient repletion, mitochondrial support, and the stress protocol. Treat varicocele, chronic endometritis, endometriosis, or structural findings on their own surgical timeline.
- 4 **Week 12–13 — Retest, because 90 days is when the answer arrives.** Repeat semen analysis with DFI, hs-CRP, homocysteine, oxidative markers, fasting insulin and HOMA-IR, hormones, thyroid, and micronutrients. Compare against baseline, not against a reference range.
- 5 **From here — keep trying on a corrected substrate, or enter ART with one.** If you proceed to IUI or IVF, you are doing it with better gametes, a better endometrium, and a lower miscarriage risk. Optimization is not an alternative to reproductive medicine; it is what makes reproductive medicine work better.

When *not* to wait

Optimization takes 90 days. Some situations do not have 90 days to spare, and in those the correct move is to run both tracks at once — start the protocol **and** get a reproductive endocrinologist or andrologist involved now.

SITUATION	ACTION
Under 35, trying <12 months	Full optimization protocol. Formal infertility evaluation at 12 months.
Age 35–39	Optimization now; formal evaluation at 6 months of trying, not 12.
Age 40 or over	Parallel-track immediately. Do not spend a year optimizing at 41 — run the protocol and see a reproductive endocrinologist in the same month.
Azoospermia or severe oligospermia	Reproductive urology / andrology now. Genetic testing, hormonal evaluation, and surgical assessment.
Amenorrhea or cycles consistently >35 or <21 days	Evaluate now — do not wait out a year of anovulatory cycles.
Known tubal disease, prior pelvic surgery, or stage III–IV endometriosis	Reproductive endocrinology now.
Two or more pregnancy losses	Full recurrent loss workup now, in parallel with the protocol.
Primary ovarian insufficiency, or AMH with rapid decline	Urgent evaluation; discuss fertility preservation immediately.
Prior chemotherapy, pelvic radiation, or gonadotoxic exposure	Evaluate and preserve now.

APPENDIX

The full *lab menu*

A consolidated ordering reference. Draw the shared panel on both partners on the same day.

DOMAIN	BOTH PARTNERS	MALE-SPECIFIC	FEMALE-SPECIFIC
Metabolic	Fasting glucose & insulin, HOMA-IR, 2-hr 75 g OGTT with insulins, HbA1c, lipids with ApoB, triglyceride:HDL, uric acid, liver panel with GGT	—	Same; run regardless of BMI in suspected PCOS
Inflammation & oxidative	hs-CRP, ferritin, fibrinogen, CBC with differential, homocysteine, F2-isoprostanes, urinary 8-OHdG, RBC glutathione	Seminal ORP (MiOXSYS)	—
Hormonal	Prolactin, DHEA-S, SHBG, total & free testosterone, estradiol	LH, FSH, sensitive estradiol, DHT, inhibin B, T:E2 ratio; 2 morning draws	Cycle day 2–5 FSH/LH/E2/17-OHP; AMH any day; post-ovulation progesterone; serial PdG
Thyroid	TSH, free T4, free T3, reverse T3, TPO & Tg antibodies	—	Target TSH <2.5 when trying
Adrenal / stress	Four-point diurnal cortisol (saliva or dried urine) with cortisone and metabolites	—	—
Micronutrient	NutrEval, SpectraCell, or Quest micronutrient panel; 25-OH vitamin D, RBC magnesium, zinc, selenium, copper:zinc, RBC folate, B12 with MMA, omega-3 index, urinary iodine	—	Ferritin with iron studies
Gut	GI-MAP or GI Effects, celiac serology (tTG-IgA + total IgA), SIBO breath test as indicated, H. pylori antigen	—	Vaginal / endometrial microbiome as indicated
Mitochondrial	Mitome or MitoSwab, organic acids, lactate:pyruvate, VO ₂ max	—	—

DOMAIN	BOTH PARTNERS	MALE-SPECIFIC	FEMALE-SPECIFIC
Toxic burden	RBC heavy metals, unprovoked urine metals, serum PFAS, urinary phthalate & BPA metabolites, environmental mold assessment	—	—
Genetic	3X4 or IntellxxDNA pathway panel; expanded carrier screening	Karyotype, Y-microdeletion, CFTR in severe male factor	Karyotype and FMR1 in DOR, POI, or recurrent loss
Structural & functional	DEXA with visceral adipose tissue and lean mass	Semen analysis ×2 with DNA fragmentation; scrotal ultrasound with Doppler; post-ejaculatory UA	Transvaginal ultrasound with antral follicle count; HSG or HyFoSy; saline sonohysterogram or hysteroscopy; CD138 biopsy as indicated
Infection & immunity	STI screen	Semen culture, seminal leukocytes	Rubella and varicella titers, hepatitis B, chlamydia antibody titer
Recurrent loss add-on	—	Sperm DNA fragmentation	Lupus anticoagulant, anticardiolipin, anti-β2GPI (×2, 12 weeks apart), ANA, thrombophilia panel

Fertility is a *vital sign*.

Treat it as one. A couple that arrives with an unexplained diagnosis has almost always been under-measured rather than genuinely mysterious — and the measurements that were skipped are, disproportionately, the ones that could have been acted on. Ninety days is not a long time to spend finding out.

This document is a clinical reference prepared by Luke Sorrell, MD, FACP for educational purposes. It is not medical advice and does not establish a physician–patient relationship. Targets described here are optimization targets, which are frequently narrower than standard laboratory reference ranges. Several tests and therapies referenced — including enclomiphene, off-label clomiphene in men, anastrozole, DHEA, and various functional laboratory panels — are used off-label, are not FDA-approved for these indications, or have limited or mixed supporting evidence, and are noted as such in the text. Any medication, supplement, or testing decision should be made with your own physician, who knows your history. Do not start, stop, or change a prescribed medication based on this document.