Peter Attia MD Keypoints — Hormones, Fertility & Sexual Health

Peter Attia MD Keypoints

Episodes in this pack: 16

410 The biology of pregnancy: physiologic adaptation, childbirth, and long-term maternal health

Guest: Dr. Kathryn (Katie) Gray
Date: 2026-10-05 · Duration: 2:01:48
URL: https://www.youtube.com/watch?v=KIFD0Y6UVE0

KEYPOINTS

• Pregnancy is a combined cardiovascular and metabolic stress test that can unmask a woman's future disease risk.
Dr. Katie Gray, a high-risk obstetrician and maternal-fetal medicine specialist at the University of Washington, frames pregnancy as an abrupt load on the heart (plasma volume expands dramatically) and on metabolism (insulin resistance rises in the second half). Women who 'fail' these tests often carry an underlying predisposition that pregnancy simply reveals early, which is why obstetric history matters for decades afterwards.

• Plasma volume rises about 50% by roughly 28 weeks, creating a relative anemia and a load some hearts can't tolerate.
Red cell mass doesn't keep pace, so hemoglobin concentration falls. Women with severe cardiac or pulmonary disease may be advised not to become pregnant at all, because standard heart-failure tools like diuretics would themselves endanger the pregnancy. Gray notes that around half of pregnancies are unplanned and the sickest patients often lack insurance and access, so disease can stay hidden until pregnancy exposes it.

• Severe pregnancy nausea appears to be driven by the GDF-15 gene, not hCG as long assumed.
Genetic studies of hyperemesis gravidarum flagged GDF-15, which is now being explored as a drug target. Fewer than 1% of pregnancies need IV fluids or nutrition, but for those women it's severe and tends to recur in later pregnancies. The main risk is maternal dehydration and malnutrition, since the fetus generally takes what it needs. Standard anti-nausea drugs can be used but often aren't enough.

• Folic acid matters before conception, because the neural tube closes before most women know they're pregnant.
Folate deficiency raises the risk of neural tube defects, and by the time a pregnancy is recognized it's too late to correct levels. Gray's referral center still sees neural tube defects monthly and saw two cases of anencephaly this year. A balanced diet plus fortified foods covers many women, but a prenatal vitamin before conception is the standard advice. Selected cases of spina bifida can now be repaired in utero, which can improve walking and bowel and bladder function.

• Gestational diabetes is an adaptive insulin resistance that overshoots, and screening is universal because risk factors missed half of cases.
Gray agrees with Attia's framing: every pregnancy shifts toward insulin resistance to route fuel to the fetus, and genes plus environment (sleep, stress, nutrition) amplify it in some women. High maternal glucose makes the fetus overgrow (macrosomia), raising the risk of C-section, shoulder dystocia, preeclampsia and newborn hypoglycemia, since the baby's own insulin keeps running after birth. Diagnosing it earlier than 24–28 weeks hasn't been shown to improve outcomes.

• Preeclampsia comes from a placenta that hasn't invaded deeply enough releasing sFlt-1, which mops up VEGF.
Normally trophoblast cells remodel the mother's spiral arteries into wide, low-pressure vessels. If that falls short, the oxygen-starved placenta releases sFlt-1, an anti-angiogenic factor that soaks up VEGF and damages endothelium in both blood vessels and kidney glomeruli. That links the hypertension and the protein in the urine. It affects about 5–7% of US pregnancies; first pregnancies and very young or older mothers are at highest risk. Untreated, it historically progressed to seizures, stroke, organ failure and death.

• Delivery is the only cure for preeclampsia, so management balances maternal risk against fetal maturity.
Blood-pressure drugs (mainly nifedipine and labetalol, chosen for safety data; ACE inhibitors and ARBs are known to harm the fetus but are used after delivery) can buy weeks. The timing of delivery depends on how severe the disease is, liver enzymes, platelets and fetal testing, not on the protein in the urine. At 37 weeks or later even mild hypertension means delivery. HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) isn't managed expectantly: give betamethasone for the baby's lungs, wait about 48 hours, deliver.

• Pregnancy complications forecast lifelong risk: about 50% of women with gestational diabetes later develop type 2 diabetes.
Preeclampsia raises later cardiovascular and kidney risk, and its strongest genetic overlap is with essential hypertension; the top hits in the first maternal genome-wide study of preeclampsia matched known blood-pressure genes. Postpartum hypertension can take 6–12 weeks to settle, may persist, or may return within 5–10 years. The pregnancy exposure itself may add risk on top of genetics, which is still being researched.

• US C-section rates have roughly tripled, and multiple C-sections raise the risk of a placenta that grows into the uterus.
Rates went from around 10% to about 30% at academic centers. Drivers include higher-risk pregnancies, repeat C-sections, maternal obesity and larger babies, and continuous fetal monitoring. Placenta accreta spectrum, where the placenta invades and won't detach, rises with each prior C-section. A low transverse incision carries under 1% rupture risk in a later labor; a vertical 'classical' incision, often needed for very premature deliveries, carries about 10%, so those women shouldn't labor.

EXAMPLES

• The sFlt-1 discovery came from a nephrologist collecting placentas.
Dr. Ananth Karumanchi at Beth Israel in Boston ran gene-expression microarrays on placentas from preeclamptic pregnancies and found sFlt-1 massively upregulated, then showed it could drive the disease. Gray, his former mentee, and Attia use it as a case for physician-scientists, and Attia links it to Judah Folkman's anti-VEGF cancer work.

• The old Down syndrome screen had a 5% positive predictive value.
Serum protein screens flagged many women, but only 1 in 20 positives actually carried a fetus with trisomy 21, which pushed many into amniocentesis. Cell-free DNA from a maternal blood draw at 9–10 weeks is far more sensitive and specific for

trisomies 21 and 18 and fetal sex, so invasive procedures have dropped.

- **Stillbirth occurs in about 1 in 160 US pregnancies.**
  Attia was startled. Stillbirth means any fetal death after 20 weeks. Even with placental pathology, autopsy and genetics, roughly half stay unexplained. A cord around the neck shows up in about a third of normal births and usually causes no harm.
- **About 20% of planned vaginal deliveries convert to C-section.**
  Gray uses this to explain why she recommends hospitals or birthing centers over home births: hemorrhage and other emergencies can arise in seconds, far from surgical backup.

OTHER RELEVANT

- **Tell every future doctor about your pregnancy complications.**
  Gestational diabetes or hypertension in pregnancy should trigger regular glucose and blood-pressure screening for life, plus serious lifestyle work. A 2-hour glucose test at the six-week postpartum visit is recommended. Primary care often never asks, so bring it up yourself.
- **Gestational diabetes treatment: diet first, then insulin quickly.**
  Targets Gray cited are fasting under 95 and 1-hour post-meal under 140 mg/dL. If more than half of readings are above target, insulin is first-line because its safety data and newborn outcomes are best; metformin is considered fairly safe but less proven. Lifestyle gets days to a couple of weeks, not months.
- **Keep exercising during pregnancy if it's going well.**
  Bed rest is bad. Don't start an intense new program, but established runners and lifters can usually continue, avoiding fall and abdominal-trauma risks like downhill skiing or riding. Women with a short cervix or threatened preterm labor may get lifting limits. Late in pregnancy, avoid lying completely flat; waking on your back isn't an emergency.
- **Don't treat breastfeeding as birth control or C-section as a microbiome failure.**
  Missing one feed can end the suppression of ovulation. Gray thinks the gut-microbiome benefits of vaginal birth are overhyped and says it shouldn't be a source of guilt.

397 - Endometriosis and adenomyosis: diagnosis, fertility, reproductive aging, & emerging treatments

Guest: Dr. Renato Tomioka
Date: 2026-06-22 · Duration: 2:00:26
URL: https://www.youtube.com/watch?v=IxHRYDM64dQ

KEYPOINTS

• Endometriosis affects about 10% of reproductive-age women (around 200 million) and is found in 30–50% of infertile women.

It's endometrium-like tissue (glands and stroma) growing outside the uterus: on the tubes, ovaries, bowel, bladder, appendix, even the diaphragm. Brazilian reproductive surgeon Dr. Renato Tomioka puts the chance of infertility with endometriosis at about 40%. Heritability is around 50%, and a mother or sister with it raises a woman's risk about sevenfold.

• Modern reproductive patterns mean about four times more retrograde menstruation than 200 years ago.

About 90% of women have some menstrual flow back through the tubes into the pelvis, but only those whose immune system (macrophages) can't clear it seem to develop disease. A woman two centuries ago, with first period at 16, first pregnancy at 20, five to seven children and two years of breastfeeding each, had around 100 cycles; today's woman has about 400. Tomioka sees hormonal suppression partly as a way to mimic that ancestral pattern. Microplastics, pollution, diet and poor sleep are suspected but unproven contributors to rising rates.

• Lesions make their own estrogen, resist progesterone and carry cancer-type mutations, but don't spread like cancer.

They overexpress aromatase, so suppressing the ovaries isn't always enough, and their progesterone receptors are downregulated, much like insulin resistance. Up to 37% of deep lesions and adenomyosis carry KRAS or PIK3CA mutations. Tomioka's analogy: a 1,000-horsepower F1 engine in a golf cart, because surrounding fibrosis and adhesions stop it from metastasizing.

• Adenomyosis, endometrial tissue inside the uterine muscle, is a separate disease affecting perhaps 20–30% of women.

It shares estrogen dominance, progesterone resistance and the same mutations, but single-cell studies show different molecular pathways. Up to 70% of women with endometriosis may also have some adenomyosis. The model is 'tissue injury and repair': the junctional zone between endometrium and muscle is breached, with miscarriage, C-section, curettage and hysteroscopy as risk factors. Once seen mainly in women in their 40s, it now shows up in younger women who have never been pregnant. It mostly causes heavy bleeding and anemia; only hysterectomy cures it.

• The '6 Ds' of endometriosis.

Dysmenorrhea (period pain that painkillers don't fix, sometimes needing IV drugs in the ER), deep dyspareunia (pain with intercourse), dyschezia (pain with bowel movements), dysuria (cyclic pain with urination), difficulty conceiving, and dysfunctional chronic pelvic pain lasting over six months. About 10% of women with endometriosis have no symptoms, or their only sign is infertility.

• Pain has three layers, and the third outlasts the disease.

Nociceptive pain from the lesion responds to surgery and hormones. Neuropathic pain from nerves invaded by lesions may need gabapentin or SNRIs and nerve-sparing surgery. Nociplastic pain (central sensitization) can persist even after a perfect surgery. Tomioka's analogy: surgery removes the burglar and hormones lock the door, but after years of ringing the rewired alarm goes off in the wind. Diagnostic delay drives that rewiring.

• Diagnosis takes 5–12 years (about 6 in the US, 7 in Brazil), and a normal routine ultrasound doesn't rule it out.

The reasons are normalization of women's pain, no blood biomarker, and a tradition of diagnostic laparoscopy. A specialist 'detailed protocol' transvaginal ultrasound with bowel prep (enema an hour before, low-residue diet, vaginal gel) can show bowel-wall layers and uses the 'sliding sign'; it takes about an hour, so few US centers offer it. MRI (non-contrast T1/T2) is also highly sensitive (around 95–98%) and better for the diaphragm and pelvic side walls but weaker for bowel lesions. Tomioka uses both before surgery.

• Hormonal therapy is first-line for pain, because surgery alone tends to recur.

For a 20-year-old not trying to conceive, start with a low-dose combined or progestin-only pill, or a hormonal IUD (Mirena or Kyleena) if she has no endometrioma and no myofascial pain, and reassess in 3–6 months. Without medication after surgery, recurrence runs about 10% a year, largely disease too small to see. One study found a Mirena after surgery cut recurrence by about 88% versus placebo. Treat it as a lifelong chronic disease, not a one-off procedure.

• Endometriosis infertility is mainly mechanical, and age outweighs everything.

Adhesions damage tube function. Older donor-egg studies found similar implantation and live-birth rates with or without endometriosis, though affected women yield fewer eggs and need more IVF cycles. Aneuploidy, mostly from egg meiosis errors, runs about 20–25% at 25, 30–35% at 30–34, about 40% at 35, 60% at 38, 70% at 40 and 80–85% after that. Very young women also have slightly more monosomies, so the curve is J-shaped with a sweet spot around 25.

• Adenomyosis lowers IVF success by about 30%, but pre-transfer suppression helps.

Failures often come at 6–8 weeks, as junctional-zone contractions expel the embryo; involvement of the junctional zone triples miscarriage risk. Two to four months of a GnRH agonist (Lupron or goserelin) before a frozen transfer, then low estrogen and high progesterone, raises implantation and live birth rates. The oral antagonists elagolix and relugolix look similar in one study but cost about $1,000 a month.

EXAMPLES

• Removing endometriomas can cut AMH by 40–50%.

These pseudo-cysts cling to the ovarian cortex where the primordial follicles sit, so stripping them takes healthy eggs too, yet the cysts also burn out follicles through iron-driven oxidative (Fenton) damage. Tomioka's answer: freeze eggs or embryos first,

then operate if the cyst is over 5–6 cm or causing pain, bowel obstruction, ureter involvement or appendix lesions.

- **A silent ureteral lesion cost one patient a kidney.**
  The endometriosis blocked her ureter and caused hydronephrosis, and a urologist removed the kidney. It's one of the 'operate even without symptoms' red flags.
- **Only about 10% of women who freeze eggs ever come back to use them.**
  In Brazil one cycle costs about $5,000 (roughly a third each for drugs, clinic and lab) plus about $150 a year storage. About 15 eggs at 25 give over 80% odds of at least one baby. Tomioka thinks 32–35 is more cost-effective; Attia argues that at 25 the downside is capped. Tomioka's typical social-freezing patient is 37–38.
- **The 40-year-old's funnel.**
  An AMH of about 1 ng/mL may yield about 8 eggs: about 75% mature, 30–60% reach blastocyst, and most of those are aneuploid, leaving perhaps one or two usable embryos. Attia calls it multiplying small numbers.
- **Mitochondrial replacement isn't 'egg rejuvenation'.**
  Two NEJM papers from a Newcastle group covered 22 patients with mitochondrial disease. Swapping the cytoplasm doesn't fix chromosome errors in the nucleus, which Tomioka calls 'a battery swap, not a new engine'. He sees eggs made from stem cells as about 10 years away.

OTHER RELEVANT

- **Push for a diagnosis if you have the 6 Ds.**
  Ask for MRI and, ideally, the bowel-prep specialist ultrasound. New 2025/26 ACOG guidance allows diagnosing and treating on symptoms alone, which may prevent progression and central sensitization in teenagers (50–75% of teens with pelvic pain have endometriosis).
- **Avoid the classic surgical mistakes.**
  Don't operate expecting to fix central sensitization; do about 8 weeks of pelvic-floor physical therapy before surgery and resume it 2–4 weeks after. Freeze eggs before removing endometriomas. Remove a damaged, fluid-filled tube (hydrosalpinx), which halves IVF success.
- **Don't delay at 40-plus by chasing natural conception after surgery.**
  Age is the dominant factor, and doctors underplay it. Check AMH early if you want children later.
- **A treatment that isn't hormonal may be coming.**
  HMI-115, a monoclonal antibody against the prolactin receptor, is in phase 3 trials for endometriosis pain.

378 Women’s health & performance: how training, nutrition, & hormones interact across life stages

Guest: Abbie Smith-Ryan
Date: 2026-01-05 · Duration: 2:24:21
URL: https://www.youtube.com/watch?v=CDsH60jt34o

KEYPOINTS

• Osteoporosis starts in childhood, so early play and lifting matter

Peter recalls a prior guest's line that osteoporosis is a childhood disease: women hit their genetic bone-density ceiling around 19 and spend the rest of life defending it. Abbie Smith-Ryan argues for broad, varied play and multiple sports rather than early specialization, plus resistance training as injury prevention — she loved Romanian deadlifts at 11 or 12 — using bands, light weights, plyometrics and med balls.

• Intense training that delays puberty costs bone, and asymmetric sports leave marks

Gymnasts, runners, swimmers and cyclists can have delayed periods, often from unintentional underfueling, and that delayed estrogen harms bone. In 15 years of DEXA scanning at UNC, Abbie says nearly every high jumper and gymnast shows a distinct spinal curve, often unknown to them — not fixable at 18–20, but something to stabilize with musculoskeletal work.

• Young female athletes need to be taught food as fuel

Rather than food rules, Abbie emphasizes adequate energy, with calorie-dense swaps (whole milk instead of skim, full-fat yogurt, nuts, seeds) for girls who can't eat much before early practice. Exercise blunts hunger, and GI distress — sometimes linked to the menstrual cycle — is common, so intake must be planned. She pushes back on the trend of protein-centric, low-carb messaging for young female athletes.

• You can train in any cycle phase; women just feel different

Her lab's data says performance largely holds across the cycle, but women feel worse in the late luteal phase: fatigue, bloating, poorer recovery and soreness. The early follicular phase brings more carbohydrate oxidation and feeling good; late follicular around ovulation is when women typically feel their best. Peak performance seems preserved; recovery is what to manage.

• Late luteal phase: prepare for the progesterone crash

Thermoregulation, water retention, inflammation and protein breakdown rise, and resting energy expenditure increases by roughly a couple hundred calories a day — just as women often eat less and the scale rises from water. Strategies Abbie mentions for symptomatic women: 2–3 g omega-3s, zinc and magnesium for sleep, more fruit and vegetables, caffeine (possibly more helpful in this phase) and creatine.

• Creatine moved fluid into cells in the luteal phase

Her lab compared phases and found creatine shifted extracellular fluid into the cell, helping with bloating and indirectly performance. Studies load at 20 g/day (four 5 g doses) for 5 days then 5 g/day; she notes midlife and brain-health data go up to 10 g. Peter says after talking with Rhonda Patrick his practice moved maintenance from 5 to 10 g. Abbie cautions creatine is helpful but not magic or the first lever for midlife women.

• Protein of about 1.6 g/kg removes most cycle concerns

A paper in review on muscle protein synthesis across the cycle suggests adequate protein (~1.6 g/kg) and amino acids around training make phase differences minor. Peter targets 2 g/kg so that misses still clear 1.6, admitting a week in Asia left him nearer 1.2. Vegetarians or older women should pay extra attention in the luteal phase.

• Perimenopause is the critical window

Abbie's work following up on the SWAN cohort finds the biggest changes in metabolism, muscle size and quality, bone and metabolic flexibility occur during perimenopause rather than after. Peter suggests tracking day-5 FSH (day 1 = period start): low when fertile, around 10 signals the transition, 25–50+ in menopause. Abbie's lab also uses daily at-home urine hormone tests to see day-to-day swings.

• Muscle quality, not just size, declines — 'ribeye versus filet'

In a two-year longitudinal study, women who followed guidance maintained muscle size but still lost quality (measured by ultrasound and pQCT, consistent with MRI), echoing Australian work by Séverine Lamon. Peter notes whether fat is intra- or intercellular matters for insulin resistance. HIIT improved metabolic flexibility regardless of hormones, and protein around exercise didn't blunt the post-exercise insulin response.

• Body composition, not weight, should be the goal

Abbie measures composition (DEXA, multi-frequency BIA or a home scale), aiming for body fat around the 25th NHANES percentile or lower, away from the 50th. For Peter's hypothetical 5'6", 150 lb, 30%-fat 40-year-old wanting 130 lb, she'd suggest ~140 lb, a modest deficit, more fiber, ~30 g protein spaced through the day, and complex carbs. She warns chronic time-restricted eating in midlife can lower metabolism and hurt protein synthesis.

• GLP-1 drugs demand resistance training and high protein

On tirzepatide or semaglutide, she'd prioritize lifting and 130–150 g protein (based on goal weight), plus amino acids around workouts. Peter prefers the lowest dose for the longest time (2.5–5 mg tirzepatide over a year); Abbie is studying checking lean mass before titrating up. She flags low energy availability on these drugs can mimic perimenopausal symptoms and may explain bone loss.

• Power declines first and matters most for falls

Citing Andy Galpin, Peter calls type 2 fiber hypertrophy central to aging: power goes first, then strength, then size. The stumbled curb is his example of why power matters. Abbie notes women may lose type 2 characteristics faster, and midlife joint pain complicates plyometrics — which Peter believes hormone therapy would often relieve.

EXAMPLES

• Nine stress fractures below ~15% body fat

As a 5'6" D2 distance runner (~115–120 lb), Abbie had nine stress fractures, all left leg/foot, each time she dropped below about 15% fat, while amenorrheic. Her bone density was actually high; she attributes it to fueling gaps and long fasting windows between twice-daily sessions.

- **Three-hour weekly plan for a busy midlife woman**

  Two 30-minute full-body lifts (6–8 reps at 60–80% 1RM, 30 s between exercises, 2 min between rounds), plus HIIT and easy cardio. For a GLP-1 recomposition case, she settled on three strength days, one HIIT and two low-intensity days, all 30 minutes.

- **10 × 1 minute on, 1 minute off**

  Her go-to HIIT, used from fit people to cancer patients: up to 10 one-minute efforts at roughly 90–110% of VO2max-level intensity — practically, a pace you couldn't hold for 1:20 — starting with six. Peter prefers RPE or ergometer power over heart rate for short intervals.

- **Pregnancy and postpartum self-tracking**

  She gained about 8% body fat per pregnancy without losing muscle, was back to baseline about six months postpartum while breastfeeding, and is unchanged eight years after her second child. She lifted (squats, lat work) until delivery, walked within days and lifted lightly within weeks.

- **Only ~19% of women resistance train**

  She cites a Bill Kraemer paper: about one in five women lift, typically once a week.

OTHER RELEVANT

- **Match time to intensity**

  Peter's reading: with lots of time, volume dominates; with ~2–3 hours a week, intensity must carry the load, so short sessions can't be phoned in. Many people who think they're doing zone 2 are really in zone 1.

- **Track your cycle and give yourself grace**

  Knowing your bleeding pattern and phase helps separate hormonal dips from problems needing a change in nutrition, medication or recovery.

- **Starting at 70 is not too late**

  For a never-exercised 70-year-old, hire a referred trainer, use machines and bands, glute activation, a push-pull for each muscle group, calves, three lifting days plus daily movement, and add submaximal carries (a minute on, a minute off).

- **Don't accept 'no' on hormone therapy**

  Peter calls the hormone-therapy retreat medicine's biggest error of the past 25 years and, citing Rachel Rubin, says being 60 and 10 years past menopause isn't automatically disqualifying; seek a competent prescriber.

374 - The evolutionary biology of testosterone: male development & sex-based behavioral differences

Guest: Carole Hooven
Date: 2025-12-01 · Duration: 2:25:41
URL: https://www.youtube.com/watch?v=rQ-LTW3c5vc

KEYPOINTS

• Sex is defined by gamete type; chromosomes determine it in mammals but don't define it across nature.
Hooven, a Harvard-trained evolutionary biologist who studied chimpanzees in Uganda, notes that birds use a different chromosome system and some reptiles use temperature. Across sexually reproducing species, sex means being organised around making sperm or eggs. That reproductive role coordinates body, hormones and average behaviour.

• XX and XY embryos are nearly identical until about weeks 5–6, when SRY switches the shared gonad toward testes.
The undifferentiated gonad can become either organ—evolution's way of not building two systems. Without SRY it becomes ovaries, though that is an active genetic process, not a passive 'default.' Testes then make testosterone, which keeps the Wolffian (male) ducts, and anti-Müllerian hormone, which removes the Müllerian (female) ducts.

• DHT gives a strong local androgen signal without flooding the fetus.
5; ×&VGV7F 6R 6öæ6VçG ated in genital tissue turns testosterone into DHT, roughly 2–5× more potent. DHT drives penis, scrotum and prostate development. In 5; ×&VGV7F 6R FVf–6–Væ7•, XY individuals may look female at birth but masculinise at puberty with normal testosterone, without facial hair or male-pattern baldness. Hooven says DHT isn't needed for male-typical muscle, which matters in sports-eligibility disputes.

• About 20% of genes on the 'silenced' second X escape inactivation, and that matters.
That partial double dose helps explain Turner syndrome (a single X): short stature, other features and usually sterility. The 70–100 Y-chromosome genes may also act in the brain before testosterone does.

• Prenatal testosterone shapes the brain; childhood testosterone barely differs.
Male fetal testosterone begins around week 8 and peaks at weeks 15–20, perhaps 400–600 ng/dL—approaching pubertal levels. 'Mini-puberty' follows, peaking around three months and fading by about six, and is linked to boys' later activity levels. Five-year-old boys and girls have almost no testosterone. So Attia's sons' rough-and-tumble play reflects how their brains were organised, not current levels.

• Above a male threshold there's little dose-response; in females small differences matter.
Men carry roughly 10–20× women's testosterone. Variation within the normal male range predicts little about sex drive or aggression, and Hooven warns you can't judge anyone by their current level. Different brain regions may have separate critical periods for sexual versus aggressive behaviour.

• Eggs are costly and sperm cheap, which drives different reproductive strategies.
A hunter-gatherer woman's lifetime output might be 8–10 children, each requiring pregnancy and nursing under energy scarcity. Men can gain from competing for status and more partners, and can 'live fast, die young' successfully; women benefit from caution and longevity. Hooven offers only a speculative idea for why eggs are made upfront and winnowed—perhaps selection.

• Rough play is adaptive and teaches boys hierarchy, limits and how to back down.
Dominance hierarchies reduce overall fighting. Male chimps play rougher, and subordinate chimps may cup a dominant's testicles to signal trust. Boys' insult-based intimacy follows a similar logic. Hooven worries phones are replacing physical play. Girls tend toward indirect reputational aggression and, she argues, lack equivalent quick conflict-resolution rituals.

• Testosterone is the ultimate cause of the male skew in violence; culture sets the rate.
About 95% of murders and roughly 98% of sexual assaults are committed by men everywhere. But Canada's lower murder rate than the US isn't a testosterone difference. Laws, religion and norms change rates while the sex gap persists. A biological tendency is not destiny.

• Involved fatherhood lowers testosterone, and that's adaptive.
Pair-bonding and hands-on care of young dependent children suppress testosterone in humans and birds. Raising it in birds makes males neglect offspring. Hooven suggests exogenous testosterone may override these social signals, with behavioural effects users don't consider.

• Estrogen does not masculinise the human brain; androgen-receptor function does.
In rodents, testosterone converted to estrogen inside the brain masculinises behaviour, but human alpha-fetoprotein doesn't sequester estrogen the same way. Aromatase-deficient men are behaviourally typical. In complete androgen insensitivity syndrome, XY people with testes and high testosterone but non-functional receptors develop as typical women, often learning the diagnosis when periods don't start.

EXAMPLES

• Graded testosterone ± aromatase inhibitor study (NEJM)
Attia recalls men chemically castrated, then given five testosterone doses with or without an aromatase inhibitor. Higher testosterone with estrogen preserved gave the best body composition, mood and libido. He argues men on physiologic TRT (about 100–150 mg/week) generally shouldn't suppress estradiol.

• Hunter-gatherer testosterone
Hunter-gatherer men peak at least a third lower than Western men, show no ~1%/year decline, and remain fertile—making Hooven sceptical that falling testosterone itself explains Western fertility trends.

• Attia's residency testosterone
At 28–30 his level was about 220 ng/dL from sleep deprivation. It normalised within a few years of leaving residency, without TRT.

- **Hooven's own hormones**
  After her ovaries were removed at 57, still producing some hormones, she noticed hair loss and plummeting libido. She now uses estrogen, progesterone and testosterone, and began lifting weights at Attia's urging.
- **The 'flick in the nuts' ratio**
  Attia's quip: across ~110 billion humans who've ever lived, boys have flicked friends' testicles countless times, versus essentially zero female equivalents. It illustrates insult-based male intimacy.

OTHER RELEVANT

- **Let kids' rough play run while it's fun**
  If they're laughing, let them work it out; intervene when someone is actually getting hurt.
- **Fix sleep, nutrition, exercise and weight before TRT—especially when young**
  Attia rarely sees a case for exogenous testosterone at 25. If treating a young man, he'd prefer hCG to preserve testicular function and fertility; TRT can permanently impair fertility and is hard to stop.
- **One man's 400 ng/dL isn't another's**
  Androgen-receptor density and CAG-repeat length vary. Change one variable at a time; if a trial to ~900 doesn't help, receptors may already be saturated. Attia wishes a clinical receptor assay existed.
- **Treat sex differences as averages with wide overlap**
  Hooven stresses huge variation—a boy who likes dolls is normal—while arguing that denying average differences distorts policy and education.

373 – Thyroid function & hypothyroidism: how new approaches are transforming care

Guest: Dr. Antonio Bianco
Date: 2025-11-17 · Duration: 2:34:14
URL: https://www.youtube.com/watch?v=jT33TbUVCGI

KEYPOINTS

• The thyroid mostly secretes inactive T4; tissues activate it into T3 as needed, and the whole system evolved to conserve iodine.

Dr. Antonio Bianco, a thyroid physician-scientist who researches how T3 shapes chromatin and gene expression, explains that receptors bind T3 strongly and T4 barely. T4 has a half-life of about 8 days and T3 about 12 hours, so activation is brief and tightly controlled. Removing an iodine from T4's outer ring makes T3; removing one from the inner ring makes reverse T3, which is inactive and can't be converted back. Iodine is recycled each step.

• Three deiodinase enzymes decide how much T3 each tissue gets.

D2 has about 1,000 times more affinity for T4 than D1 and makes roughly 80% of the T3 produced outside the thyroid. D1, in the liver and kidney, makes about 20%, clears reverse T3, and rises with insulin and carbohydrate intake. D3 only inactivates, turning T3 into T2 and T4 into reverse T3. Blood levels barely move (about 10–15%), while tissue T3 can swing tenfold within hours. Most T3 in the brain is made locally by D2.

• Fasting deliberately slows the thyroid: low insulin and leptin tell the hypothalamus to ease off.

Peter's numbers from 7–10 day quarterly fasts: TSH rose from 2 to 7, free T3 fell from 0.3 to 0.2, and reverse T3 rose from 10 to 35. Bianco explains that TSH stays 'inappropriately normal' because the hypothalamus wants to save energy, and that T4 is shunted toward reverse T3 while low D1 activity slows its clearance. Weight loss plateaus partly for this reason. The free T3/reverse T3 ratio is a decent stand-in for deiodinase activity, which can't be measured from blood.

• TSH itself causes no symptoms, and the hypothalamic control center sits outside the blood-brain barrier.

The chain runs TRH !' TSH !' T4. Symptoms come from too much or too little thyroid hormone, never from TSH itself. The mediobasal hypothalamus and pituitary are rich in D2 and read both blood T3 and locally converted T4. Diagnosis depends on TSH plus free T4. Free hormone matters because about 99.5% is bound to proteins like TBG; total T4 can read 14–15 in pregnancy while free T4 is normal.

• T3 and reverse T3 immunoassays are unreliable, especially at low levels, and mass spectrometry is needed.

The free T4 immunoassay is good, but T3 assays track mass spec only at high values and diverge below about 90–100 ng/dL. When Bianco's lab ran one sample through four reverse T3 assays, the results were 'completely crazy'. He knows of no mainstream lab offering mass spec T3, and stick to the same lab for consistency.

• Hypothyroidism affects about 20 million Americans (4–5% of adults), mostly women at about 10 to 1, and is usually autoimmune.

About 60% have TPO antibodies (Hashimoto's). Diagnosis typically needs a TSH above 10 with low free T4; a positive TPO with TSH around 4 and normal free T4 is the 'honeymoon' phase, monitored and repeated in about 3 months. Selenium, vitamin D or antioxidants may lower TPO and prolong the honeymoon, but that isn't standard care. TPO positivity alone in pregnancy raises the risk of miscarriage and prematurity.

• Graves' disease and hot nodules cause most hyperthyroidism, and the field is moving away from radioactive iodine.

In Graves' an antibody mimics TSH: palpitations, tremor, weight loss, warm sweaty hands, TSH near zero. The options are antithyroid drugs for 1–3 years (30–40% remission), surgery by a high-volume surgeon (100–150 thyroidectomies a year), or radioactive iodine, now linked to more cancers. Hot nodules don't remit, so Bianco leans toward surgery.

• Levothyroxine fixes TSH but may leave tissues like the liver hypothyroid.

T4 alone works for most patients, but in treated rats with normal TSH the liver stayed hypothyroid. Statins are the most common drug co-prescribed with levothyroxine, a hint that LDL clearance isn't fully restored. Bianco now treats hypothyroidism as a cardiometabolic risk factor requiring closer follow-up.

• For patients still symptomatic on T4, add T3, after ruling out look-alike conditions.

Symptoms aren't specific: in blinded studies they can't separate hypothyroid from euthyroid people. Menopause is the biggest confounder (he orders FSH with TSH), along with anemia, iron deficiency and obesity. A low morning temperature doesn't mean low thyroid. Secondary (central) hypothyroidism is under 1% of cases and requires a low free T4. A healthy thyroid makes about 80% T4 and 20% T3; desiccated pig thyroid has been standardized since 1985, carries about a 4:1 ratio, and is as safe as T4 alone.

EXAMPLES

• Two teachers who 'lost their jobs to hypothyroidism' changed Bianco's research.

Both had normal TSH and free T4 on levothyroxine but disabling brain fog; one said her brain stopped working the day she left the hospital after thyroid surgery. He had been sending such patients to psychotherapy. Seeing two in two weeks made him refocus his lab, which he now describes as a mea culpa.

• 1.1 million treated hypothyroid patients versus 1.1 million controls over 20 years.

His group's retrospective study found about 2.5 times higher mortality in treated patients, mostly cardiometabolic. In about 90,000 matched patients on combination therapy (half desiccated, half synthetic), mortality was 30% lower than on T4 alone. Hospitalizations in the year before diagnosis were similar between groups. Peter notes that more health-conscious patients and doctors could still confound it.

• A 1965 Brigham study by Dr. Selenkow found an optimal T4:T3 ratio of about 3.5:1.

That happens to match pig thyroid. About 1.5 million Americans take desiccated extract and about 400,000 take synthetic combinations. In blinded studies, patients prefer combination therapy.

• Peter's patient with a TSH of 74.7.

A healthy man in his 50s reached only about 13 on treatment and felt hyperthyroid at higher doses. Bianco suspects assay interference from antibodies against mouse proteins (testable) or aggregated TSH, and advises dosing to free T4 instead.

OTHER RELEVANT

• Don't treat a mildly high TSH in older adults.

After 50 the upper limit of normal rises about 1 point per decade (about 8 at 80), so a 70-year-old with TSH 6 is probably fine. At 40, a TSH of 8–9 is abnormal; look at family history, ultrasound pattern and TPO, and treatment often makes sense.

• Skip compounded 'slow-release' T3 and branded-only dogma.

No published study shows compounded T3 actually releases slowly, and dosing 5 µg accurately is hard. Brand and generic levothyroxine are equivalent (potency held to ±5%), and 40–50% of patients are switched without knowing within two years. Check FDA recall lists.

• Don't megadose iodine.

Adults need about 150 µg a day (250 in pregnancy). Japan's 500–600 µg diets come with more autoimmune thyroid disease, and excess iodine can unmask a silent nodule as hyperthyroidism.

• Watch for true slow-release T3.

A polymer form is through phase 1 with the FDA, and a T3-sulfate approach in Italy relies on steady liver conversion. Bianco also wants mass spec T3 assays made routine.

371 – Women’s sexual health: desire, arousal, and orgasms, navigating perimenopause, and more

Guest: Dr. Sally Greenwald
Date: 2025-11-03 · Duration: 2:00:42
URL: https://www.youtube.com/watch?v=_SZUHFA8KyM

KEYPOINTS

• Sexual health is part of physical health, and mismatched desire, not how often a couple has sex, predicts divorce.
OB-GYN Dr. Sally Greenwald notes the area is understudied and the data are mostly heterosexual. Orgasm shifts the body into parasympathetic mode and releases dopamine and oxytocin, and sleep metrics improve; women slept best after an orgasm with a partner, better than alone or after intimacy without orgasm. Sex burns about 6–7 METs (60–70 kcal per encounter). Among couples aged 30–60, about 20% have sex twice a week or more, about 10% not at all in the past year, and about 70% somewhere in between.

• There's a large orgasm gap: about 95% of men versus about 30% of women regularly orgasm in partnered sex.
In one-night stands the figures are about 90% for men and 12% for women. Alone, women reach orgasm in under 4 minutes on average; with a partner it takes 21–25 minutes. When foreplay lasts more than 21 minutes, over 90% of women orgasm. Arousal lengthens and widens the vagina (about 3.5 by 9 inches at rest) and changes its angle, which matters because about 30% of women have pain with intercourse.

• Most women have responsive desire rather than spontaneous desire.
Only about 15% of women feel desire in anticipation of sex; most feel it once arousal has started. That's why 'chore play', lubricant, vibrators, erotic audio or reading, and mindfulness (Lori Brotto's work) work better than waiting to be visually turned on. Emily Nagoski compares it to going to a party you weren't in the mood for and ending up enjoying it. Consent stays paramount, and stopping is always allowed.

• The clitoris is a large, wishbone-shaped, often asymmetric organ with more than 8,000 nerve endings, and most women need external stimulation.
Fewer than 10% of women orgasm from penetration alone; a clitoris-to-vaginal-opening distance under about 1 inch makes it more likely. About 10% orgasm from the internal branch on the front wall (the 'G-spot', about a third of the way in, found with a 'come hither' motion); Dr. Lauren Streicher calls the other 90% normal. One side is often more sensitive. Only 41% of Gen Z men could identify the clitoris on a diagram.

• Vibrators are evidence-based as nerves age, not a reflection on the partner.
Type A fibers, which sense vibration and deep pressure, are myelinated and age better than type C fibers, which sense light touch and heat. A couple whose usual routine stops working after decades may need an external wand or air-pulse device. Using a vibrator alone doesn't impair partnered orgasm if the technique is brought into partnered sex; 'orgasms beget orgasms' and 'sex begets sex'.

• Testosterone is the best-studied treatment for hypoactive sexual desire disorder in postmenopausal women.
The diagnosis requires more than six months of low desire that bothers the woman herself, not just her partner. Greenwald prefers a compounded daily cream on the inner thigh (or about 0.5 cc of Testim via oral syringe), aims for total testosterone above about 20 (range 20–80 ng/dL), and titrates by symptoms. Estrogen raises SHBG, which binds testosterone; more androgenic progestins blunt that rise. Estrogen therapy tends to help desire indirectly, through better sleep and fewer hot flashes.

• In perimenopause the first question is whether she wants to keep ovulating.
Some women love the energy and libido around ovulation (the late follicular phase is also a performance peak, so athletes time events to days 9–15), but 70–80% of her patients prefer not to cycle because of worsening PMS or PMDD, irregular cycles and heavy bleeding. Menopause hormone therapy doses don't suppress ovulation, while many contraceptives do. A meta-analysis of 32 trials (more than 14,000 women) found ovulation-suppressing contraception raised desire in 20%, left it unchanged in 65% and lowered it in 15%.

• Lubricant is like sunscreen for the vagina: use it every time, ideally silicone and iso-osmolar.
It reduces micro-abrasions and the pain cycles that lead to vaginismus. Vaginal osmolality is about 300; Astroglide runs about 8,000 and KY about 4,000–6,000, which pull water out of tissue. She names Uber Lube (about 600) and Good Clean Love Almost Naked (280–300). She suggests applying it about 30 minutes before sex, using an applicator to place it higher up. Nightly moisturizers (Revaree hyaluronic acid, Replens) are the 'moisturizer', and local vaginal estrogen is the 'serum'. About 30–40% of her patients on systemic hormone therapy also need local estrogen.

EXAMPLES

• Her perimenopause contraception menu.
For women who can't take estrogen: Slynd (drospirenone, a spironolactone derivative) suppresses ovulation in about 98% of women versus 50–70% for older progestin-only pills. Slynd plus an estradiol patch gives contraception with 'real' estrogen, at the cost of more breakthrough bleeding. Nextstellis pairs drospirenone with estetrol (E4), which causes less bloating and spotting, but bone data are pending. Natazia (estradiol valerate) is the only pill FDA-approved for heavy menstrual bleeding. Bioidentical-estrogen pills run about $100 a month and are rarely covered. Among synthetic pills she likes Lo Loestrin, Loestrin and Yaz/Yasmin.

• 'F* it February'.**
Couples schedule sex 2–3 times a week for the shortest month. The initiator stops fearing rejection, and the less interested partner is practicing responsive desire. She says desire stays elevated for months afterward.

• Debut survey of 1,200 high schoolers.
70% of boys described their first sex in terms of pleasure and 70% of girls in terms of pain, which is her case for teaching foreplay and lubricant early.

• The FDA-approved desire drugs are modest.

Addyi, a nightly pill taking about 6 weeks to work, added about one satisfying encounter a month over placebo; no alcohol, and it can cause nausea. Vyleesi, an injection related to PT-141 (the 'Barbie drug'), causes nausea in about 40%, can be used at most twice a week, and has been available since 2019. Sildenafil (25–50 mg) helps only specific groups: diabetics, MS, spinal cord injury and SSRI users. Where legal, 1–2 mg THC showed stronger effects in studies than either drug.

- **Sensate focus for trauma or a long break.**

Dr. Leah Millheiser's four steps: touch without breasts or genitals, then genitals without orgasm, then orgasm without penetration, then intercourse. Each stage can last a week or longer.

OTHER RELEVANT

- **Advice for partners.**

Use lube without taking it personally. Learn her anatomy, including which side is more sensitive. Invest in foreplay outside the bedroom. Near orgasm, don't change anything (about two-thirds of women want exactly the same stimulation to continue). Edging can intensify orgasm. Resources: Ian Kerner's She Comes First, Vanessa Marin's Sex Talks, OMGYes.

- **See a pelvic floor physical therapist as routine maintenance.**

A stronger pelvic floor improves orgasm, and therapy also relaxes muscles that carry pain and stress. Local vaginal estrogen is considered safe for nearly all cancer survivors.

- **Postpartum: resume sex around 6 weeks after any birth.**

High prolactin is a natural libido brake that helps space pregnancies about 18 months apart. Breastfeeding brings a menopause-like low-estrogen state in the vagina, for which she prescribes estrogen cream. Sex is safe through a healthy pregnancy unless there's a low-lying placenta or a short or weak cervix.

- **Teach kids accurate, pleasure-inclusive anatomy and consent.**

Without it, teens learn from porn. Unprotected oral sex often carries more STI risk (for example, herpes) than penetrative sex with a condom.

352 Female fertility: reproductive health, treating infertility & PCOS, and the IVF process

Guest: Paula Amato
Date: 2025-06-09 · Duration: 2:37:00
URL: https://www.youtube.com/watch?v=UvgPh7wSH94

KEYPOINTS

- **Women have a finite egg supply, and the real constraint with age is egg quality.**
  Amato, a reproductive endocrinologist in Oregon, explains that egg numbers peak in the womb. There are about 2 million at birth and about 400,000 by first period, with most lost through atresia. Eggs stay arrested mid-meiosis until the days before ovulation. Errors in splitting the chromosome pairs at that stage, which become more likely as a woman ages, produce aneuploid eggs. Even with regular ovulation, many released eggs can't make a viable pregnancy.
- **About 90% of first-trimester miscarriages come from chromosomal errors.**
  Women shouldn't blame coffee or stress for an early loss—it's almost always a 'bad split.' One miscarriage isn't usually investigated. Two in a row warrants a workup at any age, even at 40, because a treatable cause such as a uterine abnormality could be missed.
- **Infertility means a year of trying under 35, or six months over 35—and both partners get tested.**
  Roughly a third of cases are female factor, a third male, and a third combined, so a semen analysis comes early. Lifetime infertility risk is about 1 in 6. Rising rates are partly explained by delayed childbearing, with possible roles for falling sperm counts and STIs. Irregular cycles or suspected PCOS justify seeing someone before the year is up.
- **Untreated gonorrhoea and chlamydia can silently scar the fallopian tubes.**
  Ascending infection—presenting as pelvic pain, fever and discharge, though not always noticed—damages tubes without affecting the eggs or uterus, so IVF still works. Scarred tubes also raise ectopic pregnancy risk, typically presenting at 6–8 weeks; a late rupture often means removing the tube. A dye X-ray of the uterus and tubes (HSG) checks they're open.
- **PCOS affects about 6–8% of women and links irregular cycles, high androgens and insulin resistance.**
  Not trying to conceive: birth control pills suppress LH-driven ovarian testosterone, raise SHBG and protect the uterine lining from overgrowth. Long gaps between periods can lead to hyperplasia and even cancer. Patients should be screened for diabetes, often with metformin. Many women are put on the pill without being told they have PCOS and its metabolic implications.
- **For PCOS and fertility, letrozole for five days is first-line and works for most women.**
  A head-to-head randomised trial found higher pregnancy rates than with clomiphene. If there's no period, a withdrawal bleed is induced with progesterone (5–10 mg medroxyprogesterone or 200 mg micronised for 7–10 days). Letrozole runs on cycle days 3–7, with an ultrasound around day 12. About 80% of PCOS patients conceive with ovulation induction plus IUI.
- **Stop GLP-1 drugs at least two months before trying to conceive.**
  They're very effective for weight loss in PCOS, but there are no pregnancy safety data. An 'Ozempic baby' registry hasn't shown birth defects so far, but numbers are small.
- **IUI success depends heavily on age.**
  With oral drugs, per-cycle rates are about 20–25% in the 20s, 10–15% over 35 and 1–5% over 40. Multiples risk is about 5–8% with oral drugs versus 25–35% with injectables. That's why injectables with IUI—the source of tabloid 'octuplet' stories—have largely been dropped in favour of IVF.
- **IVF is a funnel, and a normal embryo implants about 70–75% of the time.**
  A typical sequence: about 10 eggs retrieved, about 70% fertilise, about half reach blastocyst by day 5–6, and genetic testing (5–6 trophectoderm cells) removes more. Single-embryo transfer is the norm because twins raise risks of preeclampsia, haemorrhage, C-section and prematurity. Donor eggs give about 70–75% success, versus 10–20% per cycle for over-40s using their own untested embryos.
- **The lab matters as much as the doctor.**
  Amato says success depends more on embryologists than physicians. Training is mostly a 4–5-year apprenticeship, and there's a national shortage. Choose clinics using SART.org clinic-specific success data (about a two-year lag) and volume—at least 100 cycles a year. Ask how genetic testing is offered. Avoid clinics that push add-ons on everyone or where you rarely see the doctor. A cycle costs about $20,000; 24 states mandate some fertility coverage, about 15 including IVF.

EXAMPLES

- **How an IVF cycle runs**
  Birth control pills sync follicles, then 8–12 days of FSH injections (with some LH) are given, along with a GnRH antagonist to block early ovulation. An hCG trigger follows, and retrieval happens 36 hours later under sedation with a 16-gauge needle through the vaginal wall into each 1.5–2 cm follicle.
- **ICSI is often used even without male factor**
  Success rates match conventional IVF when sperm are normal, but ICSI avoids the rare catastrophe of zero fertilisation. It adds about $1,000.
- **Attia's friend and a blunt gynaecologist**
  After a son was born with Down syndrome, the doctor told the mother it was 'your fault'—technically a maternal nondisjunction, but a lesson in bad bedside manner.
- **Embryo testing limits**
  Aneuploidy screening is routine. Carrier screening allows targeted testing for conditions such as CF or sickle cell. Polygenic or APOE4 selection remains controversial scientifically and ethically.
- **Future technologies**
  Lab-on-a-chip automation, in vitro maturation and making eggs from skin cells (done in mice, perhaps 10–20 years away for

humans). Mitochondrial replacement trials are running outside the US, where they're not legal.

OTHER RELEVANT

- **Egg freezing is best done in the early-to-mid 30s**
  Freezing in the 20s mostly wastes eggs you won't use. About $10,000 per cycle plus about $1,000 a year for storage; aim for 10–20 mature eggs around 30, and far more near 40.
- **Your cycle is a health signal**
  Absent, very irregular, very painful or heavy periods deserve evaluation in the teens or 20s. Overtraining or under-eating (RED-S) can stop ovulation and harm bone through low estrogen.
- **Lifestyle basics over fertility supplements**
  Amato recommends a Mediterranean diet, sleep, coping with stress and exercise without excess. Correct real deficiencies (folate, iron, vitamin D). CoQ10 and DHEA have weak evidence; she's fine with CoQ10 if it reduces stress.
- **Don't use rapamycin to extend fertility**
  A Columbia trial is testing it with AMH as the outcome, but the animal data are mixed. AMH (around 2 normal, under 1 low) reflects egg number, not quality.

351 Male fertility: optimizing reproductive health, treating infertility, & navigating TRT

Guest: Paul Turek
Date: 2025-06-02 · Duration: 2:37:18
URL: https://www.youtube.com/watch?v=RCGX5J3VQj0

KEYPOINTS

• Conception is a brutal elimination race

Of about 100 million ejaculated sperm, roughly 5 million get through the cervix past acidic vaginal fluid (pH about 5), only 100–500 reach the fallopian tube, and one reaches the egg. Turek describes research (from a company he consults for) suggesting sperm advance in waves, like a phalanx: early waves soak up the uterus's active immune response so later sperm can get through. Failing at this may explain some infertility.

• Sperm take about 74 days to make, so changes show up months later

Turek's deuterated-water study found an average of 74 days from production to ejaculation (some men as fast as 42). That includes about two weeks maturing in the epididymis, a ~35 ft tube where sperm learn to swim forward and to 'smell' follicular fluid at one part per billion. Expect any intervention to take at least 2.5 months to show results, and about 90 days for a full turnover. After varicocele repair, the average time to conception was about seven months.

• Sperm drive evolution and carry the father's environment to the next generation

Sperm stem cells divide throughout life and pick up mutations and epigenetic changes, about 50 new mutations per generation on average, with many more from older fathers. Roughly half affect brain development. About 98% of normal sperm have the right number of chromosomes, and the epididymis seems to filter out defective ones: testicular sperm show 2–3 times more abnormalities than ejaculated sperm.

• Have sex in the days before ovulation, not after

Sperm can wait in the oviduct for days, but an ovulated egg survives only about 8 hours. In a NEJM diary study of about 700 couples, sex every other day before ovulation gave the best results, and waiting until ovulation produced only about 20% of conceptions. Turek says 80% of natural conceptions come from sex in the days leading up to ovulation. For conception he advises sex every other day. For a semen analysis, abstain 2–4 days: count rises with abstinence but motility falls.

• A male workup: thorough history, expert exam, two semen analyses, hormones

Only about 23% of men get a formal evaluation before couples go to IVF in North America. Turek uses a 200-question history, which he says matters most. On exam he checks for varicocele, cancer, and a congenitally absent vas deferens (about 1 in 500 men), which he can feel and which signals a likely cystic fibrosis carrier. Semen results vary 50–100% between samples, so get at least two about three weeks apart. He reads the results like a poker hand: low motility alone points to short-term exposures, while low count plus low motility suggests something more severe.

• Testosterone therapy usually wipes out sperm production

Exogenous testosterone shuts down LH and FSH. Turek puts the chance of zero sperm at 95% for a man on injections. Topical, nasal (three times daily) and oral (twice daily) forms are more physiologic and in his experience can preserve sperm counts. hCG and clomiphene/enclomiphene stimulate the body's own production and keep fertility. He adds clomiphene when hCG goes above about 1,500 units three times a week, which starts suppressing FSH. He has about 560 men on clomiphene and argues the FDA's rejection of enclomiphene reflects the backlash over direct-to-consumer testosterone ads.

• Thick blood is the main testosterone risk

Exogenous testosterone raises EPO and red-cell mass. Turek sees events begin around hemoglobin 18 and definitely at 19, and warns of clots on long, dehydrating flights. Pellets last about four to six months. Rough symptom thresholds Turek cites: erections ~290 ng/dL, fertility ~300, libido ~350.

• Getting off testosterone: taper, then stimulate

Recovery depends on dose, duration and form: continuous injections are worst, while cycling allows recovery. Turek worries that after 5–10 years function may not return; Peter's practice treats about two years as the ceiling. Turek tapers over about six weeks, with or without clomiphene, or uses hCG plus clomiphene for a faster restart. He checks testosterone about two weeks after the last dose, as the low point. Low-dose hCG (250–500 units twice weekly) alongside testosterone kept sperm normal in a 12-week study of bodybuilders, but miss doses over years and counts can crash.

• Hot tubs are among the worst things for sperm

The testes run about 3°F cooler than the body. When infertile men stopped hot baths, total motile sperm count rose about 300% by three to four months and 600% by six. Turek estimates that 20 minutes at 104°F three times a week could take a man to zero. Saunas have about a quarter to a third of the effect (so Peter's friend's ice packs make sense), steam rooms fall in between, and cold plunges and surfing are fine.

• Other common factors

Varicoceles (about 40% of cases) come from the left testicular vein draining uphill without valves, which Turek blames on humans standing up. Hormonal problems account for 10–15%. Genetic causes include Klinefelter syndrome and Y-chromosome deletions, which don't improve with varicocele repair and are passed to sons. Alcohol and THC act as direct toxins: THC stays in fat for weeks, and two epidemiological studies tie chronic use to testicular cancer. Type 2 diabetes and obesity also matter, and a third of type 2 diabetics have low testosterone.

EXAMPLES

• Extreme training cut counts by 40%

Going from moderate exercise to two hours a day above 80% of VO2 max for 12 weeks cut sperm counts by about 40% and testosterone by about 50%, and both recovered afterward. Military stress studies showed similar drops of about 50% in LH and testosterone.

• Peter's testosterone after residency

At 33 his total testosterone was about 220 ng/dL, which Turek attributes to stress and sleep loss. Chronic stress keeps cortisol up and shuts down reproduction.

• Just being cleared had results

In Turek's USC follow-up, 65% of men he cleared conceived naturally within a year, and another 15–20% with IUI or IVF, a higher rate than any treatment he's published.

• Semen quality and lifespan

A Copenhagen study of about 74,000 men over 50 years found those with normal semen quality lived about three years longer. Turek sees semen analysis as a way into preventive health for young men.

• Mumps, Zika, Ebola and COVID

Mumps after puberty can destroy the testes. One Ebola survivor transmitted the virus sexually a year later. Among men who died of COVID, only about 1 in 7–10 autopsies found virus in the testes. Turek has seen two unexplained cases of sterility after severe COVID.

OTHER RELEVANT

• Bank sperm before chemotherapy, and consider it as you age

Turek advises every man who might want children to bank before chemo. Three normal ejaculates give roughly one child's worth for IUI. About 10 give three chances at IUI, and three are plenty for IVF. About half of frozen sperm survive thawing.

• Older fathers carry risks too

Sperm-bank guidelines treat 40 as older paternal age. Turek sees a slow linear rise in offspring risk (miscarriage, autism, schizophrenia and similar) up to about 50–60, then a steep upturn. Unlike egg chromosome problems, these single-gene mutations can't be screened out.

• Choose a bike saddle with a center cutout

Commuting cyclists in a UK study had better fertility than average, but pelvic numbness signals nerve and artery compression. Get a saddle with a cutout middle, sized to your sit bones.

• Be skeptical of testicular stem-cell or PRP injections

Offshore clinics' claims lack real controls, and Turek has found nothing after such treatments in his own surgeries.

348 Women’s sexual health, menopause, and hormone replacement therapy (HRT)

Guest: Rachel Rubin
Date: 2025-05-12 · Duration: 2:24:37
URL: https://www.youtube.com/watch?v=W0XW6av2wLQ

KEYPOINTS

• Menopause is an empty gas tank, and perimenopause is the chaos before it

Rubin calls menopause a 'castration event'. Around 52 the ovaries largely stop making estrogen, progesterone and testosterone, while men's levels fall slowly. In a typical cycle estradiol runs from about 50 pg/mL at the low point to about 150 at ovulation (pregnancy is 3,000+). In perimenopause it can swing from 200 to 900 within ten days and then drop to zero, because the brain's FSH pushes a dwindling egg supply to overshoot.

• Women vary widely in how they respond to progesterone

Rubin suspects GABA-receptor effects; nobody can predict it. When she gives micronized progesterone, about a third of patients love it (better sleep, less anxiety), a third notice nothing, and a third are sensitive (sleepy, bloated, or worse). Peter puts the bad-reaction group at 10–20%.

• Going without hormones carries real risks too

Rubin says doctors talk about the risks of medication but rarely about the risks of not taking it. Without hormones, the genital and urinary tissue loses its acidity and protective bacteria, and UTIs rise sharply. Osteoporosis follows: about as many women die from hip fractures as from breast cancer, and Peter adds that half of survivors never regain their previous function. She adds heart disease and dementia, admitting the brain data is weak.

• The WHI scare came from a press conference and relative risk

The billion-dollar trial tested one old regimen at one dose (equine estrogen, plus medroxyprogesterone with a uterus). Results were announced at a press conference before the paper came out, and hormone use fell from roughly 40% of women to almost nothing. The headline was a 24% relative rise in breast-cancer incidence in the combined arm, with no rise in breast-cancer deaths. Peter says the absolute increase was about 0.1%, roughly one extra diagnosis per 1,000 women, and calls it the greatest injustice of modern medicine in his lifetime. Unreported: fewer fractures, colon cancers and diabetes cases, lower overall mortality, and lower breast-cancer incidence and death with estrogen alone.

• A generation of doctors never learned to prescribe hormones

Fewer than 6% of internists, OB-GYNs and family doctors get even an hour of menopause training. Fewer than 4% of eligible women now use hormone therapy, which is worse than ten years ago. Rubin works out about 84 million US women over 40 and about 3,000 clinicians listed on the Menopause Society site.

• Women's testosterone falls with age, not at menopause

The decline starts in the 30s. Testosterone receptors are found in the genitals, urethra and bladder, so low levels affect more than libido. There is global consensus that it treats low libido after menopause, but the US has no FDA-approved female product (Australia has one). Rubin says the FDA demanded a second five-year study after the first showed safety, and companies quit.

• Rubin's playbook adds one hormone at a time

Both doctors usually start with transdermal estradiol, because hot flashes are the most pressing symptom and stacking shows what each drug does. Then comes progesterone: 100 mg oral micronized nightly, or 200 mg for 12–14 days a month, with Peter often going up to 200 if tolerated. Taking it vaginally can reduce sedation. Testosterone is added last. Rubin uses about a tenth of a male dose: roughly 0.5 mL of 1% gel on the calf daily, with a 5 mL tube lasting about 7–10 days. She avoids pellets: supraphysiologic and irreversible.

• Oral, patch, gel and ring estrogen each have trade-offs

Oral estrogen passes through the liver, raises clotting proteins and SHBG, and so is avoided in smokers, people with obesity, or anyone at clotting risk. The KEEPS trial found transdermal estrogen better for sexual function. Patches can fail with sauna use or heavy sweat. The Femring (0.05/0.1) is systemic and needs progesterone. The 2 mg Estring is local only. Pharmacists sometimes mix them up, and Rubin often sees levels fade in a ring's third month.

• Use labs as a guide, but trust symptoms most

Both insist on sensitive LC-MS assays for estradiol and testosterone. Peter warns that ELISA tests can be thrown off by biotin and other interference, and the better test costs maybe $5–10 more. Symptoms come first. An FSH of 78 with estradiol of 40 nudges Peter to raise the dose, and breast tenderness is his clearest sign of too much.

• Local vaginal hormones are safe and cut UTIs by more than half

Estradiol cream (about $13 a tube), the Estring, or vaginal DHEA (Intrarosa) treats genitourinary syndrome of menopause: dryness, painful sex, urgency, leakage and UTIs. Rubin says these are safe at any age, including after blood clots or breast cancer, and don't raise blood estradiol, so women on systemic therapy can add them. Her group estimates that if Medicare patients used vaginal estrogen, Medicare would save $6–22 billion a year. Yet they still carry the systemic-estrogen boxed warning.

• Neither age nor ten years of use is a reason to stop

Rubin says the timing hypothesis rests on the WHI's old drugs, and Susan Davis has recently questioned even that. She calls osteoporosis prevention 'a green light' for offering therapy at any age. She sees no evidence for stopping after ten years. Bone gains disappear quickly when hormones stop, and stopping may destabilize plaque. The one reason she accepts is an active cancer being treated by blocking hormones.

EXAMPLES

• Rubin's mother in the ICU

Over six months in a Houston ICU after a transplant, with a catheter and on ECMO, Rubin had to persuade the transplant team, the ICU team and the pharmacy every week that vaginal estrogen doesn't cause clots. She also had to teach nurses to

apply it.

- **A gynecologist's advice to a woman in her 60s**
  The woman reported painful sex and asked for vaginal estrogen. She was told to 'think of other ways' to handle her relationship.
- **The ring that went missing**
  An ultramarathoner on a ring suddenly felt awful. Her estradiol was undetectable, and she couldn't find the ring, which had probably come out during a bowel movement.
- **The brain estrogen-receptor finding**
  Rubin cites Lisa Mosconi's work: receptor density in the brain rose rather than fell after menopause, up to age 65, and tracked brain fog. Peter compares this to muscles becoming insulin resistant during fasting to save glucose for the brain.
- **Biest as 'fancy lotion'**
  Patients using compounded biest (80% estriol, 20% estradiol) sometimes have estradiol below 5. Rubin moves them to FDA-approved products she can confirm are absorbed.

OTHER RELEVANT

- **Ask for every option, and watch for red flags**
  Be wary of a clinician who offers only one product, sells you compounded hormones they profit from, pushes pellets costing thousands, or requires expensive saliva tests.
- **Find a clinician through menopause.org or isswsh.org**
  Menopause Society listing means the clinician passed an exam. ISSWSH lists clinicians focused on sexual health.
- **Consider vaginal estrogen or DHEA even if your hormone dose is good**
  Rubin says systemic estrogen often doesn't fix urinary or vaginal symptoms. Peter notes this hasn't been tested in a randomized trial, so for now it rests on expert opinion.
- **With breast-cancer risk, weigh both sides with your care team**
  After risk-reducing surgery without cancer, skipping hormones may trade breast risk for worse bone and heart outcomes. After DCIS with no endocrine therapy, Rubin sees no barrier. Active cancer needs individual decisions, and she suggests rethinking it the way prostate cancer and testosterone have been rethought.

291 Role of testosterone in men & women, performance-enhancing drugs, sustainable fat loss, & more

Guest: Derek (More Plates More Dates)
Date: 2024-02-26 · Duration: 2:48:56
URL: https://www.youtube.com/watch?v=-wkQA_oxOwA

KEYPOINTS

• Testosterone therapy for women is often dosed far too high.
Derek, the fitness and hormone commentator behind More Plates More Dates, and Peter discuss practitioners promoting cookie-cutter targets of 200–300 ng/dL total testosterone for women—levels in the male range. One woman, through a compounding error, took 10 times her dose for a month, effectively a male physiologic dose. Peter has never seen a woman in her 30s naturally in that range.

• Restore a woman's own physiology, not a population number.
Premenopausal women typically run perhaps 10–20+ ng/dL (units confuse the issue—some labs report picograms). Peter might target 80–100 ng/dL, roughly 70th–80th percentile, but notes that for a woman who naturally lived lower, even 80 may be supraphysiologic—nobody measured her at 30.

• DHEA can raise testosterone in women on oral contraceptives.
Women's androgens derive substantially from adrenal production; Derek cites papers where DHEA supplementation (25–50 mg daily) roughly quadrupled total testosterone (about 15 to 60 ng/dL) in women on the pill, which suppresses ovarian output. Even castrated men can make 30–40 ng/dL from their adrenals.

• Progesterone dosing should be individualized.
Many women can't tolerate a full 200 mg progesterone dose but feel great at 50–100 mg; the goal is finding each woman's dose while protecting the uterus from unopposed estrogen.

• Assay choice changes your numbers dramatically.
On the same blood, an immunoassay read testosterone 502 while LC-MS/MS read 381; estradiol was 41.3 by immunoassay versus 18.3 by LC-MS—more than double. Look for 'LC-MS/MS' on the report. Timing matters too: measuring three days after a TRT injection misses the peak and trough.

• For low-normal testosterone, address basics before TRT.
For a symptomatic man around 300–381 ng/dL, sleep, body fat, vitamin D and other factors can move levels 100+ ng/dL. Clomiphene and hCG can raise endogenous production—hCG might take 381 to around 1,200—and Derek expects much more clomiphene use, though bodybuilders' post-cycle regimens of 100 mg/day are absurdly high.

• FDA's Category 2 peptide list restricted compounding of popular peptides.
About 30 peptides, including BPC-157 and CJC-1295, were placed on a list the FDA said lacked sufficient safety data for compounding. Derek thinks some never should have been sold but is sad about others; he wants real trials, such as 8–12 weeks of BPC-157 in post-operative orthopedic patients.

• Myostatin inhibition is promising but expensive and modest.
A company claims follistatin gene therapy at about $25,000 per shot. In aged mice, near-complete myostatin knockdown (over 99% of mRNA) increased muscle mass about 25%. Phase 2 sarcopenia trials could matter if people over 60 gain 5–10 pounds of muscle.

• Bodybuilding prep shows how far careful dieting can go—and its hormonal cost.
Derek recommends starting with about a 300-calorie deficit and 'milking' it, with a split like 40% protein, 40% carbs, 20% fat. A natural sub-200 lb competitor may be below 2,000 calories on stage; a 260 lb pro might eat 2,500–2,600. Crash dieting from 2,800 to near nothing backfires.

• Extended fasting crushes hormones.
Peter describes how 7–10 days of water fasting dropped his testosterone from 500–600 to 100–200 ng/dL, TSH from 2 to 4–6, free T3 from about 3 to 1.5, and reverse T3 from 12 to 32.

• Supraphysiologic testosterone builds muscle even without training.
In Bhasin's classic studies, 600 mg/week (about 6x physiologic) produced the most lean mass with training—but the untrained testosterone group gained more lean mass than the training placebo group.

• Androgens like DHT shape development, so exposure timing matters.
Derek notes DHT is best known for hair loss but is central to how masculine a person becomes during development, with critical windows of exposure. Even adult women exposing themselves to androgens can push their physiology in a masculine direction—one reason supraphysiologic dosing in women can cause irreversible changes such as voice deepening.

EXAMPLES

• High-protein 'ice cream'
Derek describes a homemade blend of about 25 g whey plus 25 g casein that yields roughly 60 g of protein for about 300 calories and takes 10–20 minutes to eat.

• Cutting calories painlessly
Peter notes that dropping cooking oils and a few habits could easily remove 500–600 calories; unless you're Bryan Johnson, you probably don't want 25% of calories from oil.

• Injected carnitine
People inject L-carnitine because oral bioavailability is only about 10–15%; Derek questions whether supraphysiologic doses help those with adequate dietary intake.

• Overpriced supplements
They mock a $600 genetic test when whole-genome sequencing costs about $300, and a supplement costing $4 to make

sold at $130.

- **Wild game as lean protein**

  Peter argues hunting is practical advice: one cow elk—tags for females are often over the counter—can feed a family for more than a year, and wild game may be among the healthiest meats since the animals live unstressed. He believes rifle hunting is more humane than bow hunting because a good shot within 300–400 yards kills instantly, and it doesn't take long to become a good shot.

OTHER RELEVANT

- **Ask for LC-MS/MS hormone testing.**

  Immunoassays can overstate estradiol and testosterone, leading to bad decisions. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Women: be wary of male-range testosterone targets.**

  Aim for restoring your own physiology with a clinician who titrates carefully. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Diet with modest deficits.**

  Start around 300 calories below maintenance with high protein; aggressive cuts damage hormones and muscle.

- **Fix sleep, body fat and vitamin D before TRT.**

  These can raise testosterone meaningfully for borderline-low men. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Treat expensive 'optimization' tech skeptically.**

  From $140,000 red-light beds to pricey genetic interpretation, they suggest asking what evidence exists before paying—basics like protein, training and sleep deliver most of the benefit.

274 - Performance-enhancing drugs and hormones—risks, rewards, & broader implications for the public

Guest: Derek (More Plates More Dates)
Date: 2023-10-09 · Duration: 3:30:34
URL: https://www.youtube.com/watch?v=JNpgqpyzW98

KEYPOINTS

• Derek's own history illustrates how young men drift into steroids.
A skinny 138-pound high-school basketball player, Derek started lifting under peer pressure, later used anabolic steroids and reached 260+ pounds. At peak he estimates a combined weekly dose of about 1,500 mg to 2 g—at 20–21, 'you just think you're invincible'.

• Supraphysiologic doses don't produce proportional results.
Peter notes he's never prescribed more than about 150 mg/week of testosterone cypionate for TRT, so Derek's peak was 10–13 times that—but results were nowhere near 10–13x. At 500 mg+ per week, users often need aromatase inhibitors such as 1 mg anastrozole daily or every other day to control estrogen.

• Underground labs fill the gray market.
A vial is typically 250 mg/mL (versus pharma's 200 mg/mL increments) and costs perhaps $60–70; Chinese-sourced HGH can be about $150 for 100 IU. Quality and dosing accuracy are uncertain.

• Growth hormone secretagogues differ greatly in hunger effects.
Ipamorelin, though a ghrelin-receptor agonist, barely affects appetite, while MK-677 (ibutamoren) can drive people to eat around 2,000 extra calories a day; its half-life is roughly 24–36 hours. GHRP-6 causes acute hunger after injection. CJC-1295 with DAC has an extended half-life; most of these lack FDA approval, and some users push IGF-1 to 500+.

• Drugs dominate elite bodybuilding outcomes.
Derek ranks drugs first, then nutrition, then training—reluctantly putting numbers like 50/40/10. Physiques changed dramatically in the late 1980s–90s; growth hormone and insulin are credited for 20–30 lb lean-mass jumps, with 300 lb competitors eating around 5,000 calories and chugging 100–200 g shakes with hydrolyzed whey before workouts to avoid insulin-induced hypoglycemia.

• The cardiovascular toll is real.
They discuss deaths of young bodybuilders, including one in his 30s who did lots of cardio and ate clean, and Rich Piana, who died in his 40s with a heart reportedly around 660 g. Peter relates lipid harms to apoB and the limited tools of decades past.

• Testosterone declines gradually, not off a cliff.
After about 30–35, total testosterone falls about 1% a year and free testosterone 2–3%, varying with lifestyle—so a 45-year-old shouldn't assume a 20% drop. Some very muscular men feel fine at 450 ng/dL.

• Good TRT starts low and mimics physiology.
A reasonable starting dose is 80–120 mg/week, adjusted in fine increments like 20 mg/week. The old standard of 200 mg every two weeks produced wild peaks and troughs; daily or frequent small doses (e.g., 15 mg injected daily) or nasal Natesto avoid huge spikes to 1,500–2,000 ng/dL. Peter's clinic adjusts doses 100–120 mg/week; 'fitness-industry TRT' starts at 200 minimum.

• Estradiol shouldn't be crushed in men.
A New England Journal study around 2013–14 with 10 groups showed estrogen matters for men's fat mass and sexual function. The old idea of pinning estradiol at 20–30 pg/mL regardless of testosterone dose is outdated. Peter's T is 300–400 ng/dL with estradiol rarely above 25; he notes a higher T would bring useful estradiol too.

• hCG preserves testicular function on TRT.
To maintain intratesticular testosterone while suppressed on exogenous androgens, Derek cites about 375 IU every other day; a common starter dose is 625–750 IU twice weekly, rarely above 2,000 IU twice weekly. hCG's half-life is roughly 24–36 hours, and a study using 4,000 IU examined effects on FSH.

• Hair-loss drugs shift hormones.
Finasteride and dutasteride block conversion to DHT (a 5 mg BPH dose inhibits up to ~70% systemically), raising testosterone and estradiol by about 15–22%. By the time hair loss shows in photos, 20–30%+ may already be lost. Derek doesn't recommend the topical RU58841 given alternatives with human safety data on the horizon.

• Natural testosterone release is steady; weekly 'hammers' aren't physiologic.
Derek points out there's no situation in which healthy testes blast a man once a week with a huge dose of testosterone and its metabolites. Large, infrequent injections create spikes, then troughs with symptoms, and drive more aromatization and hematocrit rise. Smaller, more frequent dosing—or shorter-acting formulations—keeps levels closer to what the body would produce, which is why both favor it.

EXAMPLES

• Lab artifacts
Patients tested by enzyme-based assays came back with estradiol around 100 pg/mL; retested by LC-MS at LabCorp, the same men were at about 31.

• High SHBG
A man with total testosterone of 1,000 ng/dL but SHBG of 100 might have free T of only 8 ng/dL—0.8% free instead of about 2%—so total T alone misleads.

• The tennis-dad question
Peter poses a hypothetical parent wanting growth hormone to push a son from a predicted 5'10" to 6'2" for pro tennis—raising unknown risks of manipulating growth.

- **Cheap hCG**
  Derek mentions hearing of a Texas pharmacy selling 1,500 IU vials of hCG for a couple hundred dollars—cheap by his standards, though pricing varies widely by pharmacy.
- **Llewellyn's pharmacology**
  Peter recalls reading pharmacokinetic curves in an anabolics reference and thinking the then-standard 200 mg every two weeks was 'an awful idea' because of the roller-coaster levels it created.

OTHER RELEVANT

- **If considering TRT, confirm need and start low.**
  Rule out sleep, weight and other causes; use LC-MS testing and frequent small doses.
- **Don't chase estradiol down reflexively.**
  Men need estrogen; treat symptoms and accurate labs, not a number. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Understand gray-market risks.**
  Underground products vary in dose and purity; cardiovascular and hormonal costs can be severe.
- **Use hCG to preserve fertility.**
  If fertility matters, discuss hCG or alternatives before or during TRT. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Prefer modest, sustainable changes for body composition.**
  Derek's own approach to losing 10 pounds is to trim about 300 calories or find more satiating foods—not drugs. For most people, nutrition and training adjustments deliver results without the risks discussed.

260 Men’s Sexual Health: why it matters, what can go wrong, and how to fix it

Guest: Mohit Khera
Date: 2023-06-26 · Duration: 2:42:02
URL: https://www.youtube.com/watch?v=GNCpG1fkMBA

KEYPOINTS

• ED is common and largely untreated because of silence on both sides.
Khera, a Baylor urologist specialising in sexual medicine, cites a 1994 study finding about 52% of men over 40 have some ED. A rough rule: 40% at 40, 50% at 50, 60% at 60. He attributes this to accumulating health conditions more than age itself. In a recent survey of 1,500 men, about 40% had some sexual dysfunction, but only 51% had told their doctor and 44% their partner, mostly out of embarrassment. Busy primary-care doctors rarely ask. About a third of men with ED report depression and 37% anxiety because of it.

• First, tell psychological from physical ED.
Two screening questions: can you get an erection firm enough for penetration, and can you keep it until orgasm? Normal morning erections or erections during masturbation suggest a psychological cause, common in younger men, where anxiety ('I hope I don't lose it') becomes self-fulfilling. Khera uses sex therapy and daily tadalafil 5 mg to break the cycle, then often stops it. Physical causes follow the mnemonic VENT: vascular, endocrine, neurologic, trauma, plus medications like beta blockers and finasteride.

• Most physical ED starts as a 'venous leak.'
Erections depend on nitric oxide and cGMP; PDE5 inhibitors stop the enzyme that breaks cGMP down. As erectile muscle atrophies and scars with age (low testosterone and disuse contribute), the tissue can't press the veins closed, so blood flows in but won't stay. PDE5 drugs raise inflow to overcome the leak; constriction bands reduce outflow. Avanafil has the least effect on related enzymes (PDE6 affects vision, PDE11 the back) but isn't generic.

• Khera prescribes daily tadalafil as both prevention and treatment.
An as-needed pill treats one night while the disease progresses. Studies he cites suggest daily low-dose tadalafil helps maintain erectile muscle, and improved blood-vessel function persisted after stopping in a study by Aversa. 5 mg daily equals roughly 8 mg in steady state (a 1.6× multiplier). It's also FDA-approved for enlarged prostate, without the retrograde ejaculation of Flomax. Don't take it close to Flomax, which can drop blood pressure. Generic tadalafil can cost about $17 for 90 pills.

• ED is an early warning of heart disease.
In the Prostate Cancer Prevention Trial follow-up by Ian Thompson (2004), 15% of men who developed ED had a heart attack or stroke within seven years. In another study, about 50% of men with a cardiac event had ED roughly 39 months earlier. Endothelial dysfunction is the shared mechanism. In Esposito's 2004 JAMA trial of 110 obese men, a Mediterranean diet plus exercise raised ED scores by about 3 points without medication. Attia sees erections improve when patients' HbA1c falls from about 5.9 to 5.

• Peyronie's disease affects 7–9% of men and is usually linked to unnoticed trauma.
Scar plaque, often on the upper side of the shaft, causes curvature. Above 60° makes intercourse difficult. In the first year, about 15% improve, 40% stay the same and 45% worsen, so Khera waits until it stabilises before surgery. Collagenase injection (Xiaflex, 2015) is the first FDA-approved drug; vitamin E and colchicine don't work. The RestoreX traction device, used 30 minutes twice daily for 3 months, improved curvature 30–40% and can add up to about 2 cm in length (off-label, about $500). In a 2009 study, 74% of Peyronie's patients had low testosterone.

• Testosterone: treat symptoms, not just a number, and protect fertility.
Khera says total testosterone stays fairly flat in healthy men as they age, while SHBG rises and free testosterone falls. He prefers calculated free testosterone and notes androgen-receptor sensitivity varies genetically. He and Attia both decline to treat patients without symptoms. For injections he uses 50 mg cypionate under the skin twice a week (Sunday/Thursday, about $25/month), which causes less blood thickening than large doses every two weeks. Clomid raises levels but blocks estrogen, which men need for libido, in about 40%. Low-dose HCG (500 IU every other day) alongside testosterone helped preserve testicular function in Baylor studies. Nasal testosterone (Natesto) appears not to suppress sperm much.

• Khera avoids finasteride and considers post-finasteride syndrome real.
He notes that 5; ×&VGV7F 6R Ç6ò 6öàverts progesterone into allopregnanolone, a neurosteroid linked to mood and cognition. In his study of 25 men with persistent symptoms, two died by suicide. He acknowledges this is a minority view, and Attia notes randomised trials or better comparison groups are needed. For enlarged prostate he uses alpha blockers (alfuzosin has the least retrograde ejaculation) or daily tadalafil instead.

EXAMPLES

• Priapism
An erection lasting more than 4 hours needs the ER; after about 36 hours recovery is unlikely. Causes include over-dosing injections, trazodone and cocaine. Treatment: phenylephrine, draining old blood, then surgical shunts. A penile implant should go in within about 3 months, before scarring.

• Penile implants
Invented in 1973. Saline cylinders with a pump in the scrotum. Khera does about 60 a year with an infection rate near 1%, and advises choosing a surgeon who does at least 50.

• Shockwave and stem-cell clinics
Cheap radial 'shockwave' machines charge $500–$1,000 a session and, in his view, do nothing. Proper electrohydraulic or electromagnetic devices are still investigational but promising for mild–moderate ED. About 30% of men respond to placebo. No placebo-controlled stem-cell ED trial exists; his 30-man trial gained about 4 points for 6–9 months.

• Premature ejaculation
Affects up to 30% of men; about 9% of them seek care. Treatments include lidocaine spray, SSRIs (paroxetine strongest), and sex-therapy techniques (start-stop, squeeze), which can cure it. Tramadol works but is addictive. If ED and PE occur together,

treat the ED first.

OTHER RELEVANT

- **Testosterone and prostate cancer**
  The 2018 AUA guideline says there's no established link. Hopkins' bipolar androgen therapy and TRANSFORMER trial used high-dose testosterone in advanced prostate cancer, with similar survival to enzalutamide and better quality of life.
- **PSA saturation**
  PSA rises with testosterone only up to about 250 ng/dL, then levels off.
- **Orals and topicals**
  Oral undecanoate must be taken with food. Khera dislikes gels: about 20% of men barely absorb them, and they can transfer to others.
- **Testosterone reversal protocol**
  For men who want children after years on testosterone: HCG 3,000 IU plus FSH 75 IU three times weekly; sperm often returns in 3–7 months.

259 - Women's sexual health: Why it matters, what can go wrong, and how to fix it

Guest: Sharon Parish
Date: 2023-06-19 · Duration: 3:10:54
URL: https://www.youtube.com/watch?v=goLKqjUT93Q

KEYPOINTS

• Women's sexual medicine is a tiny field relative to the need

Sharon Parish has practised sexual medicine for about 30 years. She estimates the field's main annual meeting draws 500–600 people, which is probably most of the clinicians who work in it. By contrast, she jokes that the roughly 20,000 urologists at the main urology meeting all think they could handle a man's sexual problem. In the large PRESIDE survey (31,000 women aged 18–99), distressing low desire affected about 10–15% and distressing orgasm problems about 3–6%.

• Sexual function is linked to vascular and metabolic health

Peter treats erectile problems in men with prediabetes, for example an A1c of 5.9, as an early warning of blood-vessel disease. Parish says the 'female genital vascular district' may play a similar role in women and be a window into small-vessel disease, though the evidence is still being gathered. Metabolic syndrome, diabetes and obesity are associated with poorer sexual function in women too.

• Desire and arousal are different, and desire often follows arousal

Using Rosemary Basson's circular model, Parish explains that many women in long relationships don't feel spontaneous desire. Instead they start from neutral, and desire builds once arousal begins. Her first case, a married mother of two in her late 30s or early 40s who loves her partner but 'doesn't want to have sex', needs a full history covering sleep, stress, relationship, mood, menstrual and gynecologic history, and medications before any drug is considered.

• Antidepressants are a major, dose-dependent cause

About 30–40% of people on SSRIs or SNRIs develop treatment-emergent sexual dysfunction. Venlafaxine acts mostly like an SSRI at low doses (up to about 75 mg) and like an SNRI above about 100–150 mg. Parish says the best data for the fewest sexual side effects is for vilazodone, though the drug has its own drawbacks.

• Birth control pills can lower desire by raising SHBG

Every woman on combined oral contraceptives has a higher SHBG level, which binds testosterone. Ultra-low-dose (20 µg) pills are more strongly implicated than 35 µg pills. Claudia Panzer's study found that six months after stopping, former users' SHBG levels were still between those of current users and never-users. Parish wants informed consent about this before prescribing the pill, and often suggests switching to an IUD.

• Testosterone matters for women's desire, and the evidence is substantial

Women's testosterone at 18–24 roughly halves by the late 30s or early 40s, then levels off. A 2019 Lancet meta-analysis of 46 studies, 36 of them randomized, covering about 8,500 women, supports testosterone for low desire in postmenopausal women. A 300 µg patch (Intrinsa) raised testosterone and improved sexual function without worrying side effects, yet the FDA didn't approve it. Australia has an approved product, through Susan Davis's work.

• US women must improvise testosterone dosing off-label

Parish treats the syndrome, hypoactive sexual desire disorder, not a lab number. She checks baseline testosterone to rule out high levels and aims for physiological reproductive-age levels, about one-tenth of a male dose. In practice that means a roughly $200 tube of 1% gel divided into 10 piles, with blood levels checked after 3–4 weeks. She calls this 'not the kind of medicine I want to practice'.

• Two FDA-approved drugs exist for premenopausal women with low desire

Flibanserin is a daily 100 mg pill taken at bedtime that acts on serotonin and dopamine receptors. It carries an alcohol warning that has since been relaxed, and works in about 4 weeks (allow 8–12). Bremelanotide is a self-injected auto-injector used about 45 minutes before sex. About 40% of users get transient nausea on the first doses, it causes small rises in blood pressure, and rarely (about 1%) it causes focal hyperpigmentation, so she suggests no more than four doses a month.

• Orgasm problems are usually about knowledge and technique

Parish's rough split: about 30% of women reach orgasm through clitoral stimulation, about 30% through vaginal stimulation, and about 30% through either. For a 30-year-old who has never had an orgasm, she starts with education: anatomy, self-exploration, vibrators and communicating with a partner. She points patients to the OMGyes educational site (about $40 for standard programs).

• The fear of hormone therapy is largely unfounded

Parish says that even in the Women's Health Initiative, the increase in breast cancer incidence with conjugated equine estrogen plus MPA was only about 0.1% in absolute terms, with no increase in breast cancer deaths over 20+ years. Estrogen alone was associated with fewer breast cancers. Women aged 50–59 differ greatly from older starters. Hormone therapy can cut hot flashes by about 75–80%, and she calls the generation of women denied it a 'real tragedy'.

EXAMPLES

• Postpartum hormones

Breastfeeding can push estradiol down to postmenopausal levels (20–30 pg/mL), causing dryness and pain. Addressing vulvar and vaginal symptoms is often simple.

• A menopausal case

Two years after menopause (estradiol about 10, FSH about 75), Parish would discuss systemic hormone therapy (transdermal options with endometrial protection, possibly via a hormonal IUD) alongside local treatment.

• Genitourinary syndrome of menopause is progressive

Vulvar and vaginal tissue atrophy affects everyone after menopause to some degree. Local vaginal estrogen (creams, rings, inserts, tablets) or vaginal DHEA (Intrarosa) work, with no clear difference in effectiveness. Many women reach a threshold at

65–70 where lubricants are no longer enough.

- **Ageism in older women**
  Parish sees women in their 70s, 80s and 90s who want to stay sexually active. A man of 80 asking for an erectile-dysfunction drug is accepted, but a woman asking for help often isn't.

OTHER RELEVANT

- **Raise the topic with your clinician**
  Sexual problems are common, treatable and tied to overall health. If your doctor won't engage, seek out a sexual-medicine specialist or a pelvic floor physical therapist.
- **Review medications first**
  Check antidepressants and hormonal contraception before anything else. Switching contraceptive type or adjusting an antidepressant can help.
- **Don't wait for tissue damage after menopause**
  Starting low-dose local vaginal therapy early helps prevent painful sex and urinary symptoms later.

256 The endocrine system: exploring thyroid, adrenal, and sex hormones | Peter Attia, M.D.

Date: 2023-05-29 · Duration: 0:57:36
URL: https://www.youtube.com/watch?v=5oxFK6poSXM

KEYPOINTS

• The thyroid mostly makes inactive T4, which has to be converted to active T3

The hypothalamus releases TRH, which drives the pituitary to release TSH, which drives the thyroid to make mostly T4 (four iodines) and a little T3 (three). T3 does the work: keeping you warm, supporting metabolism, and maintaining hair, nails and bowel function. Deiodinase enzymes D1 and D2 remove an iodine to turn T4 into T3. D3 turns T4 into reverse T3, which Peter describes as 'anti-T3' because it blocks T3's effects.

• Reverse T3 rises sharply in some states, including fasting

Peter says his free T3 to reverse T3 ratio can fall from a normal of about 0.25 to 0.05 or below in a 5–7-day fast. He measured this before and after week-long fasts, and most of the drop came from rising reverse T3. Insulin resistance and low-grade inflammation can also shift conversion toward reverse T3, down-regulating D1 and D2 and up-regulating D3.

• Why some patients feel worse on standard T4 therapy

The textbook approach is to give a patient with a TSH of 6–7 about 75 µg of T4 and expect TSH to fall to 2–3 and symptoms to improve. Often that works. But if conversion is skewed, the extra T4 just becomes more reverse T3, so TSH looks better while the patient feels worse. For them Peter adds T3 directly, bypassing the faulty conversion step.

• How Peter gives T3

Standard immediate-release T3 (Cytomel) is hard for many patients to tolerate. He prefers compounded controlled-release T3, typically 10–30 µg, taken in the morning so it lasts through the day and fades by evening. Desiccated thyroid contains both hormones at a fixed ratio (about 4.2 units of T4 to 1 of T3), which suits some people. He usually prescribes T4 and T3 separately so each can be adjusted.

• Test more than TSH when symptoms are present

He orders TSH, free T4, free T3 and reverse T3 to infer what the deiodinases are doing. If TSH, T3 and T4 are normal and the patient has no symptoms, he skips reverse T3.

• Measure free cortisol and its metabolites over the day in urine

Most cortisol in the blood is bound to proteins, and only the free fraction acts. Peter uses the four-sample DUTCH urine test, which captures free cortisol and cortisone across 24 hours plus their breakdown products (alpha- and beta-tetrahydrocortisol, tetrahydrocortisone). Those breakdown products show total adrenal output, which a blood test can't. The healthy pattern peaks a couple of hours after waking and is low at bedtime.

• 'Adrenal fatigue' is mostly a misnomer

People who feel run down may have low free cortisol, but when total metabolized output is counted, most have ample production. The problem is often the enzyme 11;"Ô…4@, which converts between active cortisol and inactive cortisone. Insulin resistance, obesity, inflammation, low thyroid function and leptin resistance push toward cortisol. Steroid use, hyperthyroidism, progesterone, PCOS and supplements like curcumin push toward cortisone. Peter calls lifestyle management the key fix.

• Perimenopause shows up in day 3–5 FSH before periods stop

In a 28-day cycle, estradiol rises in the follicular phase, LH surges to trigger ovulation around day 14, and progesterone peaks around day 21 before falling and triggering menstruation. As ovarian output falls, the brain drives FSH and LH higher. An early-cycle FSH creeping above about 10–12 is the 'canary in the coal mine'. FSH above about 25–40, with very low estradiol, confirms menopause, and FSH can exceed 50 years later.

• Start hormone therapy during the transition, not years after

Peter doesn't wait until a woman has flat-line estradiol and very high FSH. He starts a year or two before that point, giving enough estradiol to keep FSH around 20–30. The aim is not maximal estrogen but control of hot flashes, night sweats and vaginal atrophy, and above all protection of cardiovascular and bone health. For severe PMS in women who still cycle, he uses about 50 mg of oral progesterone from day 21 to day 28, or for the full 14 days after ovulation.

• Low testosterone isn't diagnosed from a number alone

Only about 1–3% of testosterone is free, and the rest is bound to SHBG or albumin. A small fraction becomes DHT, which is 2–10 times more potent, and less than 1% becomes estrogen. Androgen receptor numbers vary between people, so a man at the 30th percentile may or may not have symptoms caused by low testosterone. In trials, testosterone improves insulin resistance and mood, but Peter remains cautious.

EXAMPLES

• Licorice that looked like Cushing's

A medical-school story: a patient who seemed to have Cushing's disease turned out to eat about 10 packs of black licorice a day. Licorice disrupts the cortisol–cortisone enzyme system, and his cortisol activity had gone through the roof.

• Phosphatidylserine for evening cortisol

For patients whose cortisol stays high at night and can't sleep, and for himself when crossing time zones, Peter uses 400–600 mg of phosphatidylserine before sleep. He says the mechanism is unclear, but he sees the effect on cortisol.

• Why he avoids Clomid for men

Clomiphene raises LH, FSH and testosterone by blocking estrogen receptors in the brain. Peter dislikes it because estrogen feedback in the brain benefits mood, and some men on it feel no better despite soaring testosterone.

• Estradiol on testosterone therapy

Peter has never seen gynecomastia in 10 years of prescribing testosterone. He avoids anastrozole unless estradiol exceeds about 50–60 or causes symptoms, because estradiol supports bone and mood.

OTHER RELEVANT

- **Peter's TRT criteria**

  There needs to be a biochemical case (free testosterone below about the 50th percentile) and, more importantly, a symptomatic case, with informed consent. He trials 8–12 weeks, moving levels to about the 80th percentile, then reassesses symptoms.

- **Understand that testosterone shuts down your own production**

  Exogenous testosterone suppresses LH and FSH. Peter warns that within a year or two, natural production can be lost for good without very large doses of synthetic LH and FSH.

- **Women should time blood tests**

  Draw FSH and estradiol on days 3–5 of the cycle during the 40s to catch perimenopause early.

253 Hormone replacement therapy and the Women’s Health Initiative: re-examining the results

Guest: JoAnn Manson
Date: 2023-05-08 · Duration: 1:20:48
URL: https://www.youtube.com/watch?v=8bRuzA-qd0s

KEYPOINTS

• The WHI tested hormone therapy for preventing disease in older women, not for treating menopause symptoms.
Manson, a Harvard endocrinologist and epidemiologist and a principal investigator of the Women's Health Initiative, explains the background. By the early 1990s, observational studies suggested women on hormones had less heart disease and cognitive decline and lower mortality. Doctors had started prescribing hormones for prevention, sometimes to women 10–30 years past menopause. Hormones were already accepted and FDA-approved for hot flashes. The open question was whether they prevented chronic disease, and no randomised trial had tested it.

• Design: two trials, about 27,000 women, average age 63.
Women aged 50–79 were enrolled: close to 17,000 with a uterus got conjugated equine estrogen plus medroxyprogesterone acetate (MPA) or placebo, and close to 10,000 without a uterus got estrogen alone or placebo. The main outcome was coronary heart disease, and the main safety outcome was breast cancer. The trial was powered to detect about a 20% heart-disease reduction. Manson corrects a common misconception: women with hot flashes weren't excluded. About 45–50% had mild to moderate symptoms, though women with severe symptoms tended to opt out. These were the formulations behind the observational data, partly because a pharmaceutical company dominated with pregnant-mare-derived estrogen.

• Manson expected a small heart benefit, not the 40–50% the observational studies showed.
Women on hormones tended to be wealthier, better educated and more health-conscious. Manson thought starting estrogen early in menopause might modestly reduce heart risk, since women's own estrogen seems to delay heart disease by about a decade compared with men. She doubted the large observational effects would hold up in a randomised trial.

• The combined-therapy arm was stopped early; the absolute breast-cancer increase was small.
Estrogen plus MPA was halted after 5.6 years, 3.3 years early, because of more breast cancer, no heart benefit, and an unfavourable overall balance across all outcomes. The relative increase in breast cancer was about 25%. Attia emphasises the absolute figures: roughly 4 versus 5 cases per 1,000 women. Manson describes most harms as about one extra case of breast cancer, heart attack or blood clot per 1,000 women per year. That's low, but it can add up with long-term use.

• Estrogen alone did not increase breast cancer; with longer follow-up it was linked to a reduction.
With estrogen alone, breast cancer fell by about 20% with longer follow-up, and breast-cancer deaths were significantly lower. With estrogen plus MPA, breast-cancer deaths trended higher but weren't significant. Breast density rose more with the combination. Manson and Attia agree the excess risk is mostly attributable to MPA. But Manson cautions that this result may be specific to conjugated estrogen, which may act partly like tamoxifen, and that other evidence (such as ovary removal lowering recurrence) still points to a role for estrogen. Total invasive cancer didn't rise in either arm, and the combination reduced endometrial cancer.

• Timing matters.
In the 2017 JAMA mortality analysis, women aged 50–59 had about a 30% lower all-cause mortality on either regimen. This wasn't significant in either trial alone. Results were neutral at 60–69. Women aged 70–79 on estrogen alone had about 22% higher mortality, borderline significant. Women in their 50s on estrogen alone also had favourable heart-attack signals. Both arms raised stroke risk, and cognition worsened in women 65 and older.

• The practice changed in a good way and a bad way.
Hormone use fell by 70–80%. Ending prescriptions for disease prevention in older women was appropriate. Extending the fear to healthy women in their 40s and 50s with distressing hot flashes was not, because their absolute risks are even lower. Attia calls it one of medicine's greatest missteps and speaks of a 'lost generation' of women, including his mother and mother-in-law. Manson says the pendulum is settling: hormones are good for some women, not all. The best candidates are healthy women in early menopause with moderate to severe symptoms.

• Manson questions Attia's case for long-term use to prevent fractures.
Attia argues that hip-fracture protection, which he estimates at about 1.5% absolute, would far outweigh a small breast-cancer increase over 30 years of use. Manson points out that bone loss resumes quickly after stopping. No subgroup at high fracture risk had a clearly favourable overall balance on combined therapy for prevention. And women who stay on hormones long-term in observational studies are a self-selected, healthier group. A 30-year trial has never been done.

EXAMPLES

• Statin use during the trial
Only 7% of participants took statins at the start, rising to over 25% during the trial. Attia notes hormones would no longer be considered for heart prevention today.

• Mammography bias
Observational studies may have overstated breast-cancer risk because women on hormones had more frequent mammograms. The WHI required one every year for everyone.

• Oral estrogen and clots
Oral estrogen passes through the liver and raises clotting proteins. This was known beforehand and was expected to be outweighed by benefits.

• Manson's H-index
About 305, one of the highest in biomedical science, according to Attia. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

OTHER RELEVANT

- **Today's formulations**
  Most women now use transdermal estradiol with micronized progesterone, or a progestin IUD. Manson favours this shift because of effects on clotting and blood pressure. But long-term outcome trials are lacking, and a new WHI-scale trial would need 40,000–50,000 women.
- **Finding a clinician**
  menopause.org (North American Menopause Society) has a zip-code search for certified menopause practitioners.
- **Non-hormonal options**
  SSRIs/SNRIs and gabapentinoids cut hot flashes by about 40–50%. A new drug that acts in the brain was awaiting FDA approval at the time.
- **Personal choice**
  Manson respects a woman's fear, for example after her mother's breast cancer, as part of the decision. Attia worries many refusals are based on misinformation.

#42–Avrum Bluming, M.D. and Carol Tavris, Ph.D.: A compelling case for hormone replacement therapy

Guest: Avrum Bluming & Carol Tavris
Date: 2020-01-08 · Duration: 2:20:36
URL: https://www.youtube.com/watch?v=njBS3s8ex24

KEYPOINTS

• Estrogen Matters argues that women have been wrongly denied HRT

Oncologist Avrum Bluming and social psychologist Carol Tavris wrote Estrogen Matters, building on their 2009 review. They argue that the belief that estrogen causes breast cancer has kept women off hormone replacement therapy for about 30 years, especially since 2002. Attia frames the episode as a story of bad science rather than a blanket endorsement. Not every woman needs HRT, and the clinical task is identifying who benefits most and for whom the risks outweigh the benefits.

• Uterine cancer scare, then the fix

Premarin (named for pregnant mare urine) was cheap to make and remains the dominant US estrogen. In the early 1970s, estrogen alone was found to raise uterine cancer risk up to about fivefold, and prescriptions fell sharply. By the late 1970s, adding a progestogen, cyclically or continuously, was shown to cancel that risk, and use climbed again. A 1991 NEJM article by Goldman and Tosteson said it was 'time for action, not debate'.

• The Women's Health Initiative enrolled the wrong population

About 16 million US women, roughly 22% of those of eligible age, used HRT in 2002. WHI participants averaged 63, about a decade past menopause. Around 70% were overweight or obese, and many smoked or had hypertension. Older women were chosen so heart events would show up sooner and cost less. Women with significant hot flashes were excluded for fear they would drop out of the placebo arm. Yet the results were 'immediately extrapolated to all women everywhere'.

• The breast-cancer finding was small and not significant

The reported 26% relative increase (hazard ratio about 1.26, later 1.24) 'almost reached nominal statistical significance'. In absolute terms, Bluming calculates it as about 0.9 extra cases per 1,000 women, under 1%. By 2006 a follow-up reported that the increased risk in that population had disappeared. Bluming and Tavris also note the WHI's leader had published 'time to bring the HRT bandwagon to a halt' beforehand. Tavris calls it confirmation bias, not a conspiracy.

• A 50–70% collapse in HRT use followed

By 2004, use had fallen from 22% to about 10%. Bluming and Tavris cite one estimate that about 50,000 women died prematurely of heart disease after stopping HRT in the years after 2002. That figure is a modelled estimate and is contested.

• The heart-disease window matters

Women who start within about 10 years of menopause, without existing cardiovascular disease, are a very different group from the WHI's 63-year-olds with existing risk factors. Attia's example is a healthy 60-year-old who went through menopause at 50 and has no evidence of heart disease.

• Bones, brain and colon

Bluming says estrogen can reduce hip fracture risk by up to 50%, better than any long-term alternative. About 21% of women who fracture a hip die within a year, roughly 40,000 a year, similar to US breast-cancer deaths. Studies, including the Nurses' Health Study, show about 20–25% less colon cancer. He says estrogen may cut Alzheimer's incidence by 20–50% depending on the study. The authors say animal, lab, field and randomised studies all point the same way on cognition.

• Breast-cancer survivors are a contested group

Bluming points to his own small 14-year study, which reported results yearly and fit alongside 14 others in showing no increased local recurrence, contralateral cancer or distant recurrence in survivors who took hormones. He notes that as early as 1944 researchers reported about a 25% response rate treating breast cancer with high-dose estrogen. He also notes progesterone did slightly better than tamoxifen in an early 1970s randomised trial. His position remains contested.

EXAMPLES

• Heart disease dwarfs breast cancer as a cause of death

Attia walks through a chart of women from age 25 onward. In every age band, a woman is more likely to die of heart disease than breast cancer over the next 10 years, from about 2–3.5 times at younger ages to about 8 times at 70 and over 12 times later.

• Attia's early-menopause patient

In August 2017, a patient had normal day-5 labs (FSH about 10, estradiol about 90) despite starting symptoms. Months later her FSH was 68 and estradiol unmeasurable. Attia rechecked, then consulted his mentor, gynaecologist Riley Lloyd. The case showed him how abruptly hormones can fall.

• Relative risks in context

From the 2009 paper, Attia reads out associations: fish intake linked to a 14% higher breast-cancer risk, and one extra weekly serving of French fries to 27%. These are comparable to the WHI's hormone signal, which nobody acts on.

• The 2003 drop in breast cancer

WHI investigators linked a 2003 fall in breast-cancer incidence to women stopping HRT. Bluming disputes the link and says the decline had begun in 1999, before the WHI was published.

• Women told to stop at 78

Bluming gets letters from former patients in their 70s and 80s, doing well on hormones, whose doctors won't renew prescriptions. Hot flashes last about seven years on average, but 10–15 for some.

OTHER RELEVANT

• Ask about absolute, not relative, risk

A '25% increase' may mean less than one extra case per 1,000 women. Ask your doctor for the absolute numbers for someone of your age and health.

• Timing and individual profile matter

Starting near menopause in a woman without cardiovascular disease differs from starting at 63 with risk factors. Decide with a clinician who knows the data, and weigh symptoms, bone, heart and family history.

• Randomised doesn't mean right

A randomised trial in the wrong population, or with the wrong formulation, can mislead. Weigh it alongside consistent observational and mechanistic evidence. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Don't stop prescriptions on age alone

Bluming argues that women benefiting from HRT shouldn't be cut off simply for turning 65 or 75. This remains debated, so review it individually.