remains unclear if this early elevation in AMH contributes to the pathogenesis of hyperandrogenemia or is an early marker of PCOS. Nonetheless, these findings suggest there are early differences in the reproductive phenotype in girls with hyperandrogenemia, even before the onset of puberty.

Reproductive Endocrinology
ANDROGENS ACROSS SEX, GENDER AND THE LIFESPAN

Erythrocytosis in a Large Cohort of Trans Men Using Testosterone: A Long Term Follow up Study on Prevalence, Determinants, and the Effect of Years of Exposure.

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Background: Erythrocytosis is a known side effect of testosterone therapy in hypogonadal men and can increase the risk of thromboembolic events. Erythrocytosis is also seen in trans men (birth-assigned female, male gender identity) receiving testosterone therapy. Currently there are no clinical guidelines for the management of this problem in trans men. **Specific aims:** 1. To study the prevalence and determinants in the development of erythrocytosis in trans men using testosterone. 2. To study the association between duration of testosterone treatment and hematocrit levels. **Methods:** A 20 year follow-up study in adult trans men who started testosterone, and had monitoring of hematocrit levels at our center (n=1073). **Results:** Erythrocytosis (defined as hematocrit levels of >0.50 l/l twice) occurred in 11% of trans men. Multilevel analyses showed former or current smoking (OR 2.2, 95%CI 1.6-3.3), testosterone administration as long-acting intramuscular injection (OR 2.9, 95% CI 1.7-5.0), a higher age at initiation of hormone therapy (up to OR 5.9, 95% CI 2.8-12.3) for people above 40 compared to <18), higher BMI (>30 g/m2 compared to 18.5-25 kg/m2) (OR 3.7, 95% CI 2.2-6.2) and a medical history for chronic pulmonary diseases, sleep apnea or polycythemia vera (OR 2.5, 95% CI 1.4-4.4) as determinants that increased the risk of high hematocrit levels. In the first year of testosterone therapy hematocrit levels increased most: from 0.39 l/l at baseline to 0.45 l/l after 1 year. Although there was only a slight continuation of this increase in the following 20 years (0.45 at 1 year and 0.46 at 20 years), the probability of developing erythrocytosis still increased (10% after 1 year, 38% after 20 years). **Conclusion:** Erythrocytosis frequently occurs in trans men using testosterone. The biggest increase in hematocrit was seen in the first year, but also after the first years there is a substantial number of people that present with hematocrit >0.50. Because smoking, obesity and use of injection as dosage form are associated with a higher risk for erythrocytosis, a reasonable first step in the care for transmen with erythrocytosis while on testosterone is to advise them to quit smoking and to switch to a transdermal administration type and if BMI is high, to lose weight.

Reproductive Endocrinology
ANDROGENS ACROSS SEX, GENDER AND THE LIFESPAN

Recovery of Male Reproductive Endocrine Function Following Prolonged Injectable Testosterone Undecanoate Treatment

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Background: Exogenous androgen treatment suppresses the hypothalamo-pituitary testicular (HPT) axis causing reduced serum LH, FSH and testosterone (T). Recovery of male reproductive endocrine function in past androgen abusers takes 9-18 months with persistent mild lowering of serum T. The natural history of recovery of HPT axis following prolonged injectable testosterone undecanoate (TU) treatment at standard dose is not known. Therefore, the Runoff Study investigated the rate and extent of reproductive hormone recovery over 12 months following cessation of 2 years of TU treatment in the Testosterone for Diabetes Mellitus (T4DM) Study, while men remain blinded to treatment allocation. **Methods:** T4DM participants without pathological hypogonadism (n=1007) were randomised to TU or Placebo (P) injections every 3 months for 2 years with 303 subsequently volunteering to enter the Runoff study at 12 weeks after last injection. Before T4DM study unblinding, they provided blood samples and validated sexual function questionnaires (PDQ, IIEF-15) at entry (3 months after last injection), 6, 12, 18, 24, 40 and 52 weeks later. Serum steroid profile (T, DHT, E_2, E_1) was measured batchwise by LCMS and serum LH, FSH and SHBG by immunoassays. **Results:** Runoff study participants in both groups were similar and did not differ from all T4DM participants. As expected, at entry to Runoff serum T was higher in TU-treated men but at all timepoints from 12 weeks onwards serum T and SHBG remained consistently 11% and 13%, respectively, lower in TU-treated than in P-treated men. Similarly, at entry sexual function scores were higher in TU-treated men but subsequently no different from P-treated men. Serum LH and FSH recovered slowly with the median time to reach their own pre-treatment baseline of serum LH was 51.1 weeks [95% CI 50.4 – 53.0 weeks] and for serum FSH was 52.7 weeks [51.0 – 60.9 weeks]. **Conclusion:** After stopping 2 years of standard dose injectable TU treatment in men without pathological hypogonadism, recovery of testicular

endocrine function is eventually complete but slow with serum gonadotropin recovery taking on 12 months since the last dose. Persistent mild, proportionate reduction in serum SHBG and T reflects lasting exogenous T effects on hepatic SHBG secretion rather than signifying androgen deficiency. This suggests that recovery from androgen-induced HPT axis suppression depends primarily on time since cessation rather than dose or duration of androgen exposure.

Reproductive Endocrinology
ANDROGENS ACROSS SEX, GENDER AND THE LIFESPAN

The Hypothalamic-Pituitary-Testicular Axis in Exceptionally Old Men

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Introduction: As life expectancy continues to increase and more men reach the extremes of age, it is important to understand the physiology of the aging hypothalamic-pituitary-testicular (HPT) axis and its role in health. While prior studies primarily focused on men younger than age ninety, we studied a unique cohort enriched for men with exceptional longevity to characterize the age-related trends in male sex-hormones, the etiology of the observed changes in the HPT axis, and its relationship with metabolic dysfunction and survival at the extremes of age. **Methods:** This is a cross-sectional study of community-dwelling Ashkenazi Jewish men (n = 427), age range 50-106 years. Longitudinal follow-up for vital status was conducted for men age ≥ 88 at enrollment (n = 86). Measurements included serum total testosterone (TT) by LC/MS, LH, SHBG, lipids, glucose and BMI. Free testosterone (FT) was calculated according to Vermeulen et. al. A change-point linear regression model was applied to describe the age trend of TT. Multivariable linear regression adjusted for comorbidities tested the associations between metabolic parameters and TT. The association between survival and TT was evaluated with the age-adjusted Cox proportional hazards model. Age-specific cutoffs for TT and LH were used to define primary and secondary hypogonadism. **Results:** The change point model was a significantly better fit for the data compared to the straight-line model (p = 0.004), indicating that TT significantly declines after age 88 years. Men age < 88 years had higher average TT (401 ± 162 vs. 278 ± 178 ng/dL, p < 0.001), FT (6.3 ± 2.0 vs. 3.3± 2.1 pg/mL, p < 0.001), and lower LH (4.3 [3.0 - 6.1] vs. 14.6 [7.2 - 25.5] mIU/mL, p < 0.001), compared to men age ≥ 88 years. The prevalence of primary and secondary hypogonadism was 2% and 11%, respectively, in men age < 88 years, and 30% and 11%, among men age ≥ 88 years (p < 0.001). A multivariable linear regression analysis revealed interactions between age, dichotomized at the change-point of 88 years, and metabolic parameters. Models stratified at age 88 demonstrated an inverse association between TT and BMI (p = 0.02), serum triglycerides (p = 0.007), and random glucose levels (p = 0.02) among men age < 88; whereas a positive association was noted between TT and HDL cholesterol (p = 0.009) in this group. In men age ≥ 88 years, TT was not associated with any of the metabolic parameters or overall survival. **Conclusions:** Low testosterone in men with exceptional longevity is largely a result of primary testicular failure that occurs around age 88 and is accompanied by preserved hypothalamic-pituitary response with no associated metabolic dysfunction or effect on survival. This is in contrast to younger men, whose low T typically results from hypothalamic-pituitary dysfunction and is associated with metabolic derangements.

Reproductive Endocrinology
FEMALE REPRODUCTIVE HEALTH: HORMONES, METABOLISM AND FERTILITY

A Simple Algorithm is Created for Identifying Intermenstrual Intervals Containing an Oscillatory LH Pattern That Associates With Vasomotor Symptoms Using Daily Urinary LH Excretion in the Study of Women's Health Across the Nation (SWAN)

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Background: A specific and unique pattern of luteinizing hormone (LH) excretion has been associated with vasomotor symptoms (VMS) in early menopausal women. Described as "oscillations" of LH excretion, this pattern is consistent with secretory "surges" of LH followed by pituitary "fatigue". This pattern has not been observed in non-VMS intermenstrual intervals and supports the concept that a breakdown in the hypothalamic-pituitary ovarian axis feed-back loops leads to extreme and cyclic variations in gonadotropin hormone releasing hormone (GnRH) secretion that stimulates collateral nerves to alter core body temperature. Regardless of the precise mechanism, the pattern of LH secretion, as transduced in daily urine as oscillations, provides the basis for the development and validation of a VMS algorithm. **Objective:** The purpose of this study was to create a simple algorithm to identify intermenstrual intervals exhibiting oscillatory LH, to facilitate investigations into its associations with VMS and other symptoms during the menopausal transition (MT). **Methods:** As part of the Study of Women's Health Across the Nation (SWAN), participants in the Daily Hormone Substudy (DHS) were asked to provide daily urine samples - from which LH, E1c, and PdG were measured - and complete a daily symptoms diary for one menstrual cycle (up to 50 days). Analyses included 144 participants whose first DHS collection did not meet the Kassam criterion for evidence of luteal activity; of these, 61 were assessed by an expert as having oscillatory LH and 83 as non-oscillatory LH. Proposed algorithm-based classifications regarding oscillatory LH included number of days with LH at least 50% of the collection maximum LH (number of large-LH days) and number of days with LH no more than twice the collection minimum LH (number of small-LH days). Agreement of these 2 criteria with rater-assigned oscillatory LH was assessed using nonparametric t-tests and binomial logistic