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

Sandra Aleksic, MD[1], Dimpi Desai, MD[2], Kenny Ye, PhD[1], Sally Duran, B.A.[1], Tina Gao, MPH[1], Jill P. Crandall, MD[1], Gil Atzmon, PhD[1], Nir Barzilai, MD[1], Sofiya Milman, MD[1].
[1]ALBERT EINSTEIN COLLEGE OF MEDICINE, Bronx, NY, USA, [2]BAYLOR COLLEGE OF MEDICINE, Houston, TX, USA.

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)

Bill L. Lasley, PhD[1], Daniel S. McConnell, PhD[2], Sybil Crawford, PhD[3].
[1]University of California - Davis, Davis, CA, USA, [2]University of MIchigan, Ann Arbor, MI, USA, [3]University of Massachusetts, Wooster, MA, USA.

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

regression. Associations of these with VMS frequency were assessed using Spearman correlations. **Results:** The number of large-LH days was strongly associated with oscillatory LH: median (interquartile range) = 13 (7,22) for oscillatory collections versus 4 (2, 11) for non-oscillatory collections (p<.0001) but number of small-LH days was unrelated (p=.98). Percentage of collection days with VMS was significantly correlated with number of large-LH days (Spearman r=.37, p<.0001) but not with number of small-LH days (Spearman r=.03, p>.05); adjustment for total collection length had negligible impact. **Conclusion:** A simple algorithm using urinary LH profiles can be used to identify intermenstrual collections that likely contain intervals of VMS.

Reproductive Endocrinology
FEMALE REPRODUCTIVE HEALTH: HORMONES, METABOLISM AND FERTILITY

Adiposity Alters Follicle Dynamics in Women of Reproductive Age With Regular Menstrual Cycles

Alexis Oldfield, B.S.[1], Brittany Y. Jarrett, PhD[2], Faith Carter, B.S.[1], Heidi Vanden Brink, PhD MS RDMS[3], Marla Elaine Lujan, PhD[4].

[1]CORNELL UNIVERSITY, Hamilton, NJ, USA, [2]Cornell University, Ithaca, NY, USA, [3]Cornell University, Kansas City, MO, USA, [4]Cornell University, ITHACA, NY, USA.

Obesity increases a woman's likelihood of experiencing adverse reproductive health outcomes, including menstrual cycle irregularity, anovulation, and luteal phase dysfunction. Despite a heightened risk of reproductive dysfunction some women with obesity display ovulatory cyclicity. The degree to which adiposity affects menstrual cycle characteristics in this population is limited to endocrine assessments; evidence supports decreased luteinizing hormone pulse amplitude and reduced luteal phase progesterone. However, these endocrine disruptions have not been linked to alterations in follicular events. The objectives of the present analysis were to evaluate longitudinal changes in follicle size populations and growth kinetics of selectable follicles (6-9mm) and identify endocrine abnormalities associated with obesity in regular cycles. 14 non-obese women (BMI <30 kg/m^2) and 15 obese women (BMI≥ 30 kg/m^2) with regular cycles were evaluated by serial ovarian transvaginal ultrasonography and venipuncture every-other-day for one complete inter-ovulatory interval (IOI). The number and diameters of all follicles ≥2 mm at each visit were documented offline using the grid method. Growth profiles of individual follicles which grew to >7mm were assessed using the Identity Method. Diagnostic, morphologic, and endocrine features were compared across groups using parametric and non-parametric t-tests (i.e. cross-sectional features) and mixed models (i.e. longitudinal features). Non-obese and obese women with regular cycles showed similar IOI, follicular phase, and luteal phase lengths. The mean number of recruitment events, maximum dominant follicle diameter, and the growth rates of ovulatory follicles over time did not differ between groups, despite confirmation of compromised mean luteal progesterone production (8.23 ng/mL vs. 14.75 ng/mL, p=0.047) and decreased mean luteal FSH levels in women with obesity (2.33 mIU/mL vs.

5.83 mIU/mL, p=0.040). Over the IOI women with obesity showed an increased proportion of 2-5 mm follicles (β=5.3%; p<0.05) and a decreased proportion of 6-9mm follicles (β=-5.0%; p=0.05) versus non-obese women consistent with fewer follicles transitioning from the 2-5 mm pool to the selectable stage. This is the first comparison of follicle dynamics between non-obese and obese women with regular ovulatory cycles. These data suggest that a smaller pool of selectable follicles is present in women with obesity and may result in suboptimal follicle development luteal function. Future studies are needed to understand the impact of altered follicle populations and luteal hormone dynamics on endometrial receptivity and fertility/fecundity.

Reproductive Endocrinology
FEMALE REPRODUCTIVE HEALTH: HORMONES, METABOLISM AND FERTILITY

An Oral Contraceptive Containing Estetrol 15 MG and Drospirenone 3 MG Has Limited Effects on Endocrine and Metabolic Parameters

Christine Klipping, MD, PhD[1], Ingrid JM Duijkers, MD, PhD[1], Maud Jost, PhD[2], Adriana Bastidas, MD[2], Jean Michel F. Foidart, MD, PhD[3].

[1]Dinox bv, Groningen, Netherlands, [2]Estetra, an affiliate's company of Mithra Pharmaceuticals, Liège, Belgium, [3]University of Liège, Liège, Belgium.

Background: Most combined oral contraceptives (COCs) contain ethinylestradiol (EE), an estrogen component known to increase the risk of venous thromboembolic events. Previous phase 2 trials have shown that Estetrol (E4), a naturally-occurring estrogen produced by the human fetal liver, in combination with Drospirenone (DRSP), inhibits ovulation and is associated with favorable vaginal bleeding, safety and tolerability profiles and high user satisfaction. When administered in doses up to 10 mg for less than 3 months, E4 either alone or in combination with DRSP showed limited effects on liver function as well as on metabolic and endocrine parameters. However, the impact of E4 15 mg/DRSP 3 mg, the selected dose for pregnancy prevention (hereafter referred to as E4/DRSP), on metabolic and endocrine parameters was never investigated. **Methods:** A randomized, open-label, controlled, three-arm parallel study was conducted in 101 healthy volunteers aged 18-50 years with a body mass index between 18.0 and 30.0 kg/m^2. Of the randomized individuals, 98 subjects received either E4/DRSP (n=38), EE 30 μg/levonorgestrel (LNG) 150 μg (n=29) or EE 20 μg/ DRSP 3 mg (n=31) COCs for six consecutive treatment cycles of 28 days. Endocrine and metabolic parameters were measured at baseline, cycle 3 and cycle 6. **Results:** FSH and LH decreased with both EE/LNG (-84% and -92%, respectively) and EE/DRSP (-64% and -90%, respectively), whereas E4/DRSP slightly increased FSH (31%) and had minor effect on LH (-8%). Total cortisol increased by more than 100% during treatment with EE/LNG (109%) and EE/DRSP (107%), while E4/DRSP only slightly increased total cortisol (26%). The effects of E4/DRSP, EE/LNG and EE/DRSP on other endocrine parameters including androstenedione (-31%, -49% and -40%) and free testosterone (-50%, -50% and -71%) were similar. Liver proteins, except