Conclusions: This pilot study confirms heterogeneity in practice patterns and variable interactions of women with TS with the healthcare system, especially as patients enter adulthood. Although some women were referred to subspecialists, our initial data uncover patient uncertainty about healthcare and transition recommendations. Our preliminary data indicate the need for early patient education in a collaborative, multi-disciplinary fashion. We plan to validate and extend our initial findings by reviewing additional medical records. Ultimately, we plan for expanded education, consistent surveillance recommendations, and planned transition of patients with TS from pediatrics to adult caregivers.

Reproductive Endocrinology

FEMALE REPRODUCTIVE HEALTH: HORMONES, METABOLISM AND FERTILITY

Obese Women Exhibit Reduced Inhibin B and Estradiol SecretionFollowing Pulsatile Intravenous FSH Administration

Thanh Ha Luu, MD, Katherine Kuhn, MS, Andrew P. Bradford, BSC, PhD, Rachel Johnson, MS, Nichole Carlson, PhD, T Rajendra Kumar, PhD, Alex Joel Polotsky, MD, MS.
University of Colorado, Aurora, CO, USA.

Introduction: Maternal obesity is an independent risk factor for reduced reproductive fitness. Decreased secretion of FSH in women with obesity is well documented but poorly understood. Furthermore, obese women secrete less protein and steroid hormones from their ovaries. In mice, prior studies have demonstrated that pulsatile release of FSH enhances ovarian function and fertility.
Hypothesis: We hypothesize that insufficient FSH pulsatility, as seen in women with obesity, results in inadequate folliculogenesis and reduced ovarian steroid production. We attempt to correct pulsatile FSH secretion in obese women by administering exogenous FSH to compensate for the suppressed circulating ovarian hormones. Our primary outcome is the change in peak inhibin B between pre- and post-treatment. We present results from our interim analysis.
Methods: Reproductive aged, regularly menstruating, normal weight (NW) (BMI 18.5-24.9) and obese (OB) (BMI >30) women were recruited for a 26hr study during the early follicular phase. Frequent blood sampling (q10min) for 10h was performed to obtain baseline hormone levels. At 10h, 3 mg of cetrorelix, a gonadotropin hormone antagonist, was given followed by a secondary dose (0.25mg) 6h later. At this time, hourly IV recombinant (r)FSH (30IU) was initiated and frequent blood sampling continued for 10h. LH, FSH, estradiol (E2) were measured by immunoassay (Advia Centaur XP, Siemens). Inhibin B was measured using an ELISA kit (Ansh labs). Differences between groups were modeled by linear regression, adjusted for age and cycle day (continuous). The relationship between change in peak inhibin B and change in peak E2 was estimated in a linear regression.
Results: A total of 36 participants (19 NW and 17 OB) were included in our interim analysis. There were no differences in age, cycle day of study, race, and waist/hip ratio. Inhibin B and E2 rises following the intervention were statistically significant within each group. Peak Inhibin B and E2 levels following intervention were lower in obese women compared to normal weight (133.4 vs 202.5 pg/mL and 85.8 vs 126.4 pg/mL, respectively). The difference in pre and post peak inhibin B levels trended lower in the obese group (-40.1 (95%CI: -86.2, 6.1, p=0.087). No difference was seen in maximal E2 response. There was no relationship between inhibin B and E2 response [0.08 (95%CI -0.26, 0.42), p=0.634].
Conclusions: These early results suggest obese women may have a lower response to pulsatile rFSH as compared to normal weight counterparts even with intravenous administration. We speculate this may be due to decreased uptake of rFSH in obese patients or a sign of ovarian dysfunction in obese women. Additional subjects are recruited to detect these differences.

Reproductive Endocrinology

FEMALE REPRODUCTIVE HEALTH: HORMONES, METABOLISM AND FERTILITY

Serum Concentrations of GDF9 and BMP15 Across the Menstrual Cycle

Angelique Helena Riepsamen, PhD[1], Mark W. Donoghoe, PhD[2], Angela Baerwald, PhD[3], Michael W. Pankhurst, PhD[4], Shelly Lien, BSci[1], Yih Harng Chong, PhD[4], David Mark Robertson, PhD[1], William L. Ledger, MB ChB, PhD, FRANZCOG[1], Robert B. Gilchrist, PhD[1].
[1]Fertility & Research Centre, University of New South Wales, Sydney, Australia, [2]Stats Central, Mark Wainwright Analytical Centre, University of New South Wales, Sydney, Australia, [3]University of Saskatchewan, Saskatoon, SK, Canada, [4]University of Otago, Dunedin, New Zealand.

Growth differentiation factor-9 (GDF9) and bone morphogenetic protein-15 (BMP15) are TGF-β proteins that regulate key processes throughout folliculogenesis and are determinants of mammalian fecundity (1). They are uniquely produced predominantly by the oocyte and have potential clinical application as markers of oocyte quality and quantity (2). However, no studies have been conducted to assess whether serum concentrations alter across the different phases of the menstrual cycle, and thus if assessment should be confined to specific cycle stages. The aim of this study was to measure serum concentrations of these proteins during the menstrual cycle in women at different stages of reproductive life. Serum was collected every 1-3 days throughout the menstrual cycle from 41 healthy ovulatory women from three cohorts: menses to late luteal phase (21-29 years of age; n=16; University of Otago) and across one interovulatory interval (18-35 years of age; n=10; and 45-50 years of age; n=15; University of Saskatchewan), with simultaneous ultrasound scans confirming ovulation. Serum concentrations of GDF9, BMP15, estradiol, FSH, LH, progesterone, inhibin A and B and AMH were measured. GDF9 and BMP15 were detectable in 54% and 73% of women and varied 236- and 52-fold between women, respectively. To detect changes, mean concentrations and variances across the cycle were statistically modelled using a generalized additive model of location, shape and scale (GAMLSS). Across the menstrual cycle, there were minimal changes in serum GDF9 or BMP15 within a woman for all

cohorts, with no significant differences detected in modelled mean concentrations. However, modelled variances were highest in the luteal phases of all women for BMP15 immediately following ovulation, regardless of age, suggesting a possible underlying cyclic pattern. These results suggest that serum BMP15 and GDF9 are not overtly affected by menstrual cycle dynamics but may be more stable in the follicular phase. Larger studies with more frequent sampling should establish if BMP15 and presumably GDF9 demonstrate clinically relevant cyclic variation.
References: (1) Gilchrist RB et al., HRU 2008; 14:159-77. (2) Riepsamen AH et al., Endocrinol 2019; 160:2298-313.

Reproductive Endocrinology

FEMALE REPRODUCTIVE HEALTH: HORMONES, METABOLISM AND FERTILITY

The Effect of Estetrol/Drospirenone on Ovarian Function Is Similar to a Well-Established Combined Oral Contraceptive: Results From a Phase 2 Study

Ingrid JM Duijkers, MD, PhD[1], Christine Klipping, 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: Combined oral contraceptives (COCs) often contain ethinylestradiol (EE), an estrogen known to be associated with several side effects including venous thromboembolism. Estetrol (E4) is a native estrogen synthesized by the human fetal liver during pregnancy. Results from a phase 2 dose-finding study showed that E4 15 mg in combination with drospirenone 3 mg (E4/DRSP) resulted in a good bleeding profile and cycle control. Here, we present phase 2 results showing the effect of E4/DRSP on ovarian function. **Study Design:** A single-center, randomized, open-label, parallel study was conducted in healthy young volunteers with proven ovulatory cycles. Study subjects received either E4 15 mg/DRSP 3 mg (n=41) or EE 20 µg/DRSP 3 mg (n=41) in a 24/4-day regimen for three consecutive cycles. Both in cycle 1 and 3, serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH), estradiol and progesterone levels were determined, and follicular size and endometrial thickness were measured every three days using transvaginal ultrasound. Ovarian function was assessed using the Hoogland score, which considers follicular size and estradiol/progesterone levels. Return of ovulation was determined after treatment cessation. Safety and tolerability were assessed by monitoring adverse events (AEs), vital signs, physical and gynecological examination, clinical laboratory parameters, 12-lead electrocardiogram and echocardiogram. **Results:** No ovulations were reported during the use of E4/DRSP, while three ovulations occurred in two subjects in the EE/DRSP group. In both groups, most participants had no ovarian activity according to the Hoogland score. In cycle 1, Hoogland scores and follicular diameters were similar in both groups. In cycle 3, these parameters were slightly less suppressed in the E4/DRSP group when compared to EE/DRSP. While mean FSH and LH concentrations were less inhibited by E4/DRSP, mean estradiol and progesterone concentrations and endometrial thickness were similarly suppressed in both groups. Return of ovulation occurred on average 15.5 days after discontinuation of E4/DRSP intake. The number of frequently reported AEs considered to be related to study medication was similar for both treatment groups except for breast pain (11 subjects in the E4/DRSP group *versus* 4 subjects with EE/DRSP). Most related AEs were of mild or moderate intensity. Three subjects discontinued due to an AE, one with E4/DRSP (severe stress, emotional lability), and two with EE/DRSP (emotional lability, depressed mood). Other safety assessments did not show significant abnormalities. No serious AEs were reported. **Conclusions:** The combination of E4 15 mg and DRSP 3 mg results in adequate ovulation inhibition and ovarian function suppression, which is similar to a well-established COC containing EE/DRSP. E4/DRSP is considered safe and well-tolerated.

Reproductive Endocrinology

FEMALE REPRODUCTIVE HEALTH: HORMONES, METABOLISM AND FERTILITY

The Impact of the Covid-19 Pandemic on Women's Reproductive Health

Lisa A. Owens, MD[1], Niamh Phelan, MD[1], Lucy Ann A. Behan, MD[2].
[1]St James's Hospital/Trinity College Dublin, Dublin, Ireland, [2]Tallaght University Hospital/Trinity College Dublin, Dublin, Ireland.

Background: The Covid-19 pandemic has profoundly affected the lives of the global population. It is known that periods of stress and psychological distress can affect women's menstrual cycles. We, therefore, performed an observational study of women's reproductive health over the course of the pandemic. **Materials & Methods:** An anonymous digital survey was shared by the authors via social media in September 2020. All women of reproductive age were invited to complete the survey. **Results:** 1031 women completed the survey. The mean age was 36.7 ± 6.6 years. 693/70% reported recording their cycles using an app or diary. 233/23% were using hormonal contraception. 441/46% reported a change in their menstrual cycle since the beginning of the pandemic. 483/53% reported worsening premenstrual symptoms, 100/18% reported new menorrhagia (p=0.003) and 173/30% new dysmenorrhea (p<0.0001) compared to before the pandemic. 72/9% reported missed periods who not previously missed periods (p=0.003) and the median number of missed periods was 2 (IQR 1-3). 17/21% of those who 'occasionally' missed periods pre-pandemic missed periods 'often' during the pandemic. 467/45% reported a reduced libido. There was no change in the median cycle length (28 days) or days of bleeding (5) but there was a wider variability of cycle length (p=0.01) and a 1-day median decrease in the minimum (p<0.0001) and maximum (p=0.009) cycle length. Women reported a median 2kg increase in self-reported weight and a 30-minute increase in median weekly exercise. 517/50% of women stated that their diet was worse and 232/23% that it was better than before the pandemic. 407/40% reported working more and 169/16% were working less. Women related a significant increase in low mood (p<0.0001), poor appetite (p<0.0001), binge eating (p<0.0001), poor concentration (p<0.0001), anxiety (p<0.0001), poor sleep (p<0.0001),