loneliness (p<0.0001) and excess alcohol use (p<0.0001). Specific stressors reported included work stress (499/48%), difficulty accessing healthcare (254/25%), change in financial (201/19%) and living (169/16%) situation, difficulties with homeschooling children (191/19%), family or partner conflict (170/16%), family illness or bereavement (156/15%), and difficulties accessing or providing childcare (99/10%). **Conclusions:** The Covid-19 pandemic has significantly impacted the reproductive health of women. The long term health implications of this are yet to be determined and future studies should address this.

Reproductive Endocrinology

FEMALE REPRODUCTIVE HEALTH: HORMONES, METABOLISM AND FERTILITY

Vitamin D and TSH: Do Their Level Impact on IVF outcomes?

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Abstract: There is a positive correlation between serum 25 (OH) Vit D concentrations below 30 ng/ml and the incidence of preterm delivery, while higher levels can bring benefits to pregnancy. Although studies agree that TSH levels affect fertility, in euthyroid women (0.5<TSH<4.5), the serum concentration of this hormone still has a dubious effect on gestational outcomes. In order to study the relationship between vitamin D, TSH levels and pregnancy endpoint, a retrospective cohort study was conducted that considered 520 women who had undergone In-Vitro Fertilization (IVF). Patients were grouped regarding TSH values in mIU/L: 0.5-2.49 (Group 1) (n=416) and 2.5-4.5 (Group 2) (n=104), the serum levels of 25 (OH) Vit D within them were dichotomized in subgroups: <30 ng/mL (Group 1, n=212; Group 2, n=49) and >30 ng/mL (Group 1, n=204; Group 2, n=55). Primary endpoint was clinical pregnancy (the presence of the gestational sac and fetal heartbeat by ultrasound) and secondary outcomes were miscarriage and gestacional age (preterm or full-term pregnancy). The rate of clinical pregnancy in group 1 was significantly higher in patients with 25 (OH) Vit D <30 ng/ml (51.9%) than 25 (OH) Vit D >30 ng/ml (42.2%) according to the chi-square test and Fisher's exact test (p<0.05 all). There was no significant difference in group 2 (p=0.35), with percentages of 49% and 40% in the respective subgroups. Moreover, no statistical difference between the abortion rates was seen in 25 (OH) Vit D subgroups in groups 1 (p=0.71) and 2 (p=0.52). When gestational age rates were measured, the percentage of full-term pregnancies was lower in patients with 25 (OH) Vit D <30 ng/ml (Group 1=62.6%; Group 2=57.9%), compared to those with 25 (OH) Vit D >30 ng/ml (Group 1=77.6%; Group 2=78.9%), however, only the subgroups in the TSH category between 0.5-2.49 mUI/L showed a statistically significant difference (p<0,05). The Spearman test identified a weak positive correlation between 25 (OH) Vit D and gestational age (ρ=0.218; p<0.05). The findings indicate lower frequency of clinical pregnancy in patients with TSH between 0.5-2.49 mIU/L and 25 (OH) Vit D >30 ng/ml. In addition, variations in 25 (OH) Vit D, in both TSH groups, do not suggest interference in miscarriage rates. Furthermore, higher serum concentrations of 25 (OH) Vit D seem to be involved with an increase in the prevalence of full-term births, an important finding to guide the procedures for IVF.

Reproductive Endocrinology

HYPERANDROGENIC DISORDERS THROUGHOUT THE LIFESPAN AND INTO THE NEXT GENERATION

11-oxyandrogen Concentrations in Adolescents With Polycystic Ovary Syndrome (PCOS)

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PCOS is common in adolescents and includes excess testosterone concentrations. The clinical importance of 11-oxyandrogens in PCOS is unclear. We sought to determine if fasted morning 11-oxyandrogens: 1) better identify PCOS diagnosis compared to testosterone, 2) relate to clinical comorbidities of PCOS, 3) are altered with combined oral contraceptive pill (COCP) or metformin therapy. Data from 186 adolescent females aged 12-21 years, mostly obese, enrolled in one of 6 studies in our division were included: 115 untreated PCOS (13 lean, BMI 22.5±2.2 kg/m2; 102 overweight/obese, BMI 35.4±5.3), 9 obese PCOS treated with COCP (BMI 33.7±5.7), 6 obese PCOS treated with metformin (BMI 36.4±5.3) and 70 normally cycling controls (19 lean, BMI 19.9±1.4; 52 overweight/obese BMI 35.5±10.4). Three 11-oxyandrogens (11-hydroxyandrostenedione (11OHA), 11-hydroxytestosterone (11OHT), and 11-ketotestosterone (11KT) and total testosterone were analyzed via liquid chromatography tandem mass spectroscopy (LabCorp/Esoterix, Calabasas, CA). Data between 1) untreated PCOS and controls and 2) untreated PCOS and the 2 treatment groups were compared. ROC analysis was performed to evaluate accuracy of diagnosis of PCOS and Pearson's correlation coefficient was calculated for 11-oxyandrogens and clinical measures. Untreated PCOS girls had higher 11OHA (129±77 ng/dL PCOS vs 97±52 control, p=0.003) and 11OHT (13.8±7.9 ng/dL PCOS vs 10.5±6.7 control, p=0.005) compared to controls, with no difference in 11KT (30.7±17.3 ng/dL PCOS vs 26.6±16.6 control, p=0.208). Only 11OHA remained significant after controlling for obesity via multiple linear regression. However, neither of these metabolites better predicted PCOS status compared to testosterone (ROC analysis: 11OHA AUC=0.620, p=0.006; 11OHT AUC=0.638, p=0.002; total testosterone AUC=0.840, p<0.001, free androgen index AUC 0.860, p<0.001). Among girls with PCOS, all three 11-oxyandrogens correlated with hirsutism severity as graded by Ferriman Gallwey score. COCP treatment decreased 11KT concentrations compared to untreated PCOS (32±17 untreated vs 17±8 ng/dL COCP; p=0.039) as well as total testosterone (46.9±21 untreated

vs 28.1±12.9 ng/dL COCP; p<0.006). However, metformin treatment had no effect 11-oxyandrogens, although total testosterone was lower (46.9±21 untreated vs 26.5±5.9 metformin; p=0.01). Whereas 11-oxyandrogens would not aid in the diagnosis of PCOS, they relate to excess hair growth and 11KT decreases with COCP therapy. Further work is needed to determine the relationship with metabolic outcomes and the clinical utility of measuring these androgens in PCOS.

Reproductive Endocrinology

HYPERANDROGENIC DISORDERS THROUGHOUT THE LIFESPAN AND INTO THE NEXT GENERATION

Ambient Circulating LH, but Not Insulin, Predicts Rise in Testosterone Levels After Recombinant hCG in Girls With Obesity

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Polycystic ovary syndrome (PCOS) is associated with obesity and insulin resistance. Adolescent hyperandrogenemia (HA) may precede adult PCOS. Androgen production in females occurs in both the adrenals and the ovaries, but the relative contribution of each to adolescent HA is unknown. Both luteinizing hormone (LH) and insulin contribute to HA in adult PCOS, and both correlate with HA in obese girls, but detailed assessments of LH and insulin in combination with ovarian and adrenal androgen responses to stimulation (in the same individual) have not been described. To assess the relative roles of stimulatory factors (LH and insulin) and end organ (adrenal, ovarian) responsiveness to stimulation, we have studied 16 girls with obesity: age 13.4 (10.5–15.9) y (median [range]); Tanner 5 (2 girls 2-3; 14 girls 4-5); BMI Z 2.2 (1.7–2.7); free testosterone (T) 17.7 (6.6–88.3) pmol/L. Subjects underwent a detailed study including (a) frequent blood sampling for LH (6p–9a), to estimate mean 24-h LH; (b) sampling for insulin from 1 h before to 2 h after a standardized mixed meal (7p) and while fasting (7a–9a), to estimate mean 24-h insulin; (c) an adrenal stimulation protocol (dexamethasone [DEX] given at 10p, with 17-OHProgesterone [17OHP], T, and androstenedione (Δ4A) drawn before plus 30 and 60 min after synthetic ACTH [250 mcg iv] given at 7a); and (d) an ovarian stimulation protocol (after the 8a sample above, recombinant hCG [r-hCG, 25 mcg iv] given, DEX given at 10p, with 17OHP, T, and Δ4A drawn the next morning at 8a). Responses to ACTH and r-hCG stimulation were defined as the mean value 30 and 60 min post-ACTH and the value 24 h post-hCG, respectively, minus the post-DEX morning value. Relationships between such responses and estimated mean 24-h LH and 24-h insulin were assessed using Spearman partial correlation (correcting for differences in 24-h insulin and 24-h LH, respectively). Estimated 24-h LH was 3.7 (1.8–21.5) mIU/mL in the group, while estimated 24-h insulin was 61.4 (23.2–175) uIU/mL. After correcting for differences in 24-h insulin, estimated 24-h LH predicted hCG-stimulated changes in T (r = 0.61, p = 0.02), but did not predict ACTH-stimulated changes in T. When corrected for 24-h LH, there were no significant relationships between estimated 24-h insulin and T responses to either r-hCG or ACTH. Estimated 24-h LH and 24-h insulin were not correlated with ACTH- or hCG-stimulated changes in either 17OHP or Δ4A. These data suggest that, in pubertal girls with obesity, either that ovarian T responses to stimulation are influenced by ambient LH concentrations, but not by insulin, or that ovarian hyperresponsiveness leads to increased LH. Similar relationships with 17OHP or Δ4A were not evident, for either ambient LH or insulin. Simultaneous detailed assessments of LH, insulin, and end organ (adrenal, ovarian) responsiveness to stimulation may help discriminate the determinants of HA in girls with obesity.

Reproductive Endocrinology

HYPERANDROGENIC DISORDERS THROUGHOUT THE LIFESPAN AND INTO THE NEXT GENERATION

Anti-Mullerian Hormone Protein-Altering Variants Are Associated With Hypertriglyceridemia in the General Population

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We found 17 rare PCOS-specific functional protein-altering variants (PAVs) or mutations in the gene, *AMH*, that decrease the biologic activity of the encoded protein, anti-Müllerian hormone (AMH), in the heterozygous state. Approximately 3% of European ancestry PCOS cases in our cohort of ~700 were affected. Our preliminary studies found evidence for a metabolic phenotype in both PCOS as well as their male first-degree relatives who were heterozygous carriers of these *AMH* PAVs. We performed this study to test the hypothesis that *AMH* mutations are associated with metabolic abnormalities in the general population. The Mount Sinai BioMe Biobank is an electronic health record (EHR)-linked biobank, containing anonymized whole exome sequences from 30,813 participants of diverse ancestries. We interrogated the sequence data to identify individuals with PCOS-related *AMH* PAVs. IRB-approval was obtained to review the linked EHR. Outcomes were the presence of obesity (BMI ≥ 30 kg/m^2), type 2 diabetes (hemoglobin A1C ≥ 6.5%), prediabetes (hemoglobin A1C 5.7% - 6.4%), elevated cholesterol (total cholesterol ≥ 200 mg/dL), hypertriglyceridemia (TG ≥ 150 mg/dL), and hypertension (≥2 blood pressure values ≥140/90, or administration of antihypertensive medications). Control subjects were obtained from the National Health and Nutrition Examination Survey using propensity score matching (for sex, age, and BMI) with a 1:4 case:control ratio. A total of