1.1 ng/mL Thyroid function tests were in the normal range. hCG was negative. A random progesterone was 12 ng/mL, consistent with an ovulatory cycle. Her ovarian assessment showed FSH of 6.6 IU/L, LH of 6.7 IU/L, estradiol of 51 pg/mL, Inhibin B of 139 pg/mL, all in the normal range. Transvaginal pelvic ultrasound determined the ovarian volumes to be 8 and 6 mL, respectively, with a basal antral follicle count of 15 per side. This would have predicted a normal AMH level in this patient. However, AMH levels were repeatedly found to be low (0.05 to 0.1 ng/mL) using the pro-Mature AMH assay. As this patient was interested in future fertility, additional studies to further investigate her AMH production were carried out.

AMH Measurement: Novel AMH ELISAs with antibody epitopes specific to Pro-Mature, Mature-Mature and Pro-Pro were used to analyze the sample. The observed AMH concentration by Pro-AMH ELISA, Mature-Mature ELISA and PCOCheck ELISAs were 0.1 ng/mL, 0.14 ng/mL, and 4.99 ng/mL, respectively. AMH Pro-Pro assay (PCOCheck) uses a linear epitope two-sided antibody that is not impacted by post-translational modifications, known AMH mutations or conformational changes due to thermal instability.

Conclusions: The AMH measurements indicate that the patient's serum may not contain pro-mature associated form of AMH or the C-fragmented AMH in circulation. This may be due to mutated AMH in the C-terminus and can result in C-truncation. This subject's AMH is mostly fragmented and contains enriched pro-region AMH, which was measured by PCOCheck ELISA.

The Teaching: Tests such as PCOCheck ELISA, targeted to specific regions of AMH will provide clinicians better tools for patient management. Such tests will also help resolve the observed AMH discrepancies with AFC using legacy AMH tests. PCOCheck ELISA can be a valuable tool for assessment of ovarian reserve or polycystic ovary syndrome (PCOS).

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HYPERANDROGENIC DISORDERS THROUGHOUT THE LIFESPAN AND INTO THE NEXT GENERATION

Progesterone Positive Feedback on Pulsatile LH Secretion and FSH Release May Be Blunted in Estradiol-Pretreated Women With PCOS

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In women pretreated with estradiol (E2), exogenous progesterone (P4) acutely augments LH and FSH release (P4 positive feedback). Women with PCOS exhibit impaired P4 negative feedback on LH pulse frequency, but it remains unclear whether such women exhibit impaired P4 positive feedback on LH/FSH release. We sought to explore the latter notion as an *a priori* secondary hypothesis in a study primarily designed to assess whether P4 acutely suppresses LH pulse frequency. We studied 12 women with PCOS and 12 normally-cycling, non-hyperandrogenic controls. After 3 days of transdermal E2 pretreatment (0.2 mg/day), subjects were admitted to the Clinical Research Unit (CRU) for a 24-hour frequent blood sampling protocol starting at 2000 h. (CRU admissions occurred no earlier than cycle day 7 in PCOS and between days 7 and 11 inclusive in controls.) At 0600 h, subjects received either 100 mg oral micronized P4 or placebo (PBO). In a subsequent menstrual cycle, subjects underwent an identical CRU protocol except that P4 was exchanged for PBO or vice versa. LH secretion was analyzed using Autodecon, a deconvolution program that provides estimates of LH pulse frequency, pulsatile LH secretion (amount of LH secreted as pulses), and basal (non-pulsatile) LH secretion. Results were analyzed using 2-period crossover design analysis of covariance. In both groups, neither LH pulse frequency nor basal LH secretion changed significantly with P4 (compared to changes with PBO). Mean LH increased with P4 in both groups—3.1-fold (95% CI, 2.4–4.0) in controls and 2.7-fold (95% CI, 2.1–3.5) in PCOS; in both groups, P4-related changes were significantly greater than PBO-related changes (Bonferroni-corrected p=0.012 and 0.010, respectively). In controls, pulsatile LH secretion increased 3.5-fold (95% CI, 2.3–5.2) with P4—significantly more than with PBO (p=0.029); while in PCOS, a 2.6-fold (95% CI, 1.8–3.9) increase with P4 was not significantly different from changes with PBO (p=0.911). In controls, mean FSH increased 2.0-fold (95% CI, 1.7–2.3) with P4—significantly more than with PBO (p=0.004); but in PCOS, a 1.5-fold (95% CI, 1.3–1.8) increase was not significantly different from changes with PBO (p=0.072). Despite the above, between-group (PCOS vs. controls) differences in P4-induced changes in pulsatile LH secretion and mean FSH were not formally (statistically) demonstrable. Between-group differences representing potential confounders included age (median 25.5 vs. 19.0 y; p=0.029), body mass index (29.9 vs. 21.8 kg/m2; p=0.006), and cycle day of CRU admissions (day 45.0 vs. 10.4 for P4 admissions; 30.0 vs. 10.0 for PBO admissions). In summary, these data suggest that P4-induced increases in pulsatile LH secretion and mean FSH may be blunted in PCOS compared to controls, which could contribute to ovulatory dysfunction in PCOS. However, our results do not confirm this possibility, and further study is needed.

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Skeletal Muscle Health in Polycystic Ovary Syndrome: Protective Effect of Hyperandrogenism or Detrimental Effect of Insulin Resistance? A Systematic Review and Meta-Analysis

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Women with polycystic ovary syndrome (PCOS) exhibit reduced skeletal muscle insulin-mediated glucose uptake. Altered muscle mass may affect insulin resistance (IR) and inflammation, thereby potentially aggravating reproductive status including ovulatory cyclicity and fertility potential. However, the relationship between PCOS and skeletal muscle mass is elusive given conflicting reports on protective or detrimental influence of PCOS endocrine derangements (hyperandrogenism, IR) on muscle. We evaluated whether muscle mass and function are affected by PCOS in response to a call to elucidate musculoskeletal alterations in the International Evidence-based Guideline for the Assessment and Management of PCOS. Databases of MEDLINE, Web of Science, and Scopus were searched (January 1990 to September 2020) to identify observational studies on skeletal muscle mass (lean tissue mass) and function (strength) in PCOS and control groups. The primary outcome was total lean body mass (LBM) or fat-free mass (FFM). Data were pooled by random-effects models and expressed as weighted mean differences and 95% confidence intervals. Forty-five studies (n = 3,676 [1,854, PCOS; 1,822, controls]) were eligible. Forty-one evaluated lean tissue mass and five strength. PCOS groups had increased total (0.83 [0.08, 1.58] kg; P=0.03; I^2 = 72.0%) yet comparable trunk (0.84 [-0.37, 2.05] kg; P = 0.15; I^2 = 73.0%) LBM/FFM. There were no associations between mean differences of groups in total testosterone (TT) or homeostatic model assessment of IR (HOMA-IR) and total/trunk LBM/FFM (All: P ≥ 0.75) by meta-regressions. However, mean differences of groups in body mass index (BMI) were associated with total (0.65 [0.23, 1.06] kg; P < 0.01; I^2 = 56.9%) and trunk (0.56 [0.11, 1.01] kg; P = 0.02; I^2 = 42.8%) LBM/FFM. Accordingly, PCOS sub-group with overweight/obesity (BMI ≥ 25 kg/m^2) exhibited greater total LBM/FFM than controls (1.58 [0.82, 2.34] kg; P < 0.01; I^2 = 64.0%) unlike a lean (BMI < 25 kg/m^2) sub-group (-0.45 [-1.94, 1.05] kg; P = 0.53; I^2 = 69.5%). Some study results were contradictory (i.e., increased appendicular mass or strength in PCOS group or comparable findings between groups) and study methodology varied; thus, inclusion in meta-analyses was not possible. PCOS cohorts have a tendency for increased total and trunk lean tissue mass likely attributed to obesity. However, most critically, whether PCOS influences other lean tissue areas (appendicular), morphology, and function is unclear. Our observations do not support any protective/detrimental influence of hyperandrogenism (TT) or IR (HOMA-IR) on lean mass. Heterogeneity among studies warrants research to address any contributions of lifestyle, healthcare, and biological factors to observed differences for future guideline recommendations to improve PCOS musculoskeletal and reproductive health (www.crd.york.ac.uk/PROSPERO ID, CRD42020203490).

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HYPERANDROGENIC DISORDERS THROUGHOUT THE LIFESPAN AND INTO THE NEXT GENERATION

Sleep Characteristics Among Women With and Without PCOS

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Clinical studies indicate that sleep disorders, including obstructive sleep apnea (OSA) and excessive daytime sleepiness, occur more frequently among women with PCOS compared to comparison groups without the syndrome. The presence of OSA in PCOS is associated with worsening of metabolic parameters. There is some evidence that obesity directly contributes to OSA among women with PCOS, although, it does not fully account for findings from community-and clinic-based studies. Questionnaires are used as screening for sleep disorders. The objective was to verify the quality of sleep, the prevalence of OSA and daytime sleepness among women with PCOS compared to control group. The sample size calculation was based on estimates bad quality of sleep among women with PCOS in 80% and among control women in 45% (1). The sample with 58 women, 29 each group, had a power of 80%, with a significance level of 0.05. This is a cross sectional study with 29 patients with PCOS and 31 controls from Gynecology Endocrinology Ambulatory of São Vicente de Paulo Hospital, Passo Fundo, RS, Brazil, who consulted between January 2017 and March 2020. Women with PCOS by Rotterdam criteria and controls were under 40 years old and no pregnant. Controls women had regular cycles, no history of PCOS or hirsutism and had normal ovaries on transvaginal ultrasound. Age, BMI, blood pressure (BP), waist circumference (WC) were measured. It was applied the validated questionnaires of Pittsburgh Sleep Quality Index, to classify in good and bad sleep quality; Epworth Sleepiness Scale for daytime sleepiness and Berlim Questionnaire for evaluate sleep apnea risk. The mean of age was 30.6 ± 5.9, PCOS 29.1± 6.7 versus 32.3±4.7, p=0.06. The group of PCOS women was heavier (BMI 32.4±6.1versus 28.0 ± 5.3, p=0.04) and presented higher WC (101.3±16.1 versus 91.6 ±14cm, p=0.03). The mean of BP was similar between the groups. The prevalence of bad sleep quality was 53.6% for women with PCOS and 63.1% for controls (p=0.29). The daytime sleepiness was present in 14,5% of the women with PCOS and 35.7% of controls (p=0,061) and the sleep apnea risk was 32.1% for women with PCOS and 21.4% for controls (p=0.27). The association of risk of OSA was verified with robust multivariate Poisson. The prevalence ratio (PR) of BMI ≥ 30 was 1.820 (CI 1.281-2.587) p<0.001, BMI ≥ 25 1.549 (IC 1.067- 2.250) p=0.02, adjusted for age, WC and PCOS diagnosis. In conclusion, there was no difference in prevalence of quality of sleep, OSA risk or daytime sleepiness between women with PCOS and controls. The risk of OSA was higher in obese women independently of age, abdominal circumference and PCOS diagnosis.

Reference: (1) Fernandez et al., Nature and Science of Sleep 2018; 10: 45–64.

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